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CANCER RESEARCH

A MONTHLY JOURNAL OF ARTICLES AND ABSTRACTS REPORTING CANCER RESEARCH

VOLUME 4 DECEMBER, 1944 NUMBER 12

Ribonucleic Acid and Heterochromatin in Epidermal Carcinogenesis*

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(Received for publication June 15, 1944)

An important function of the system composed of heterochromatin, nucleolus, and nuclear membrane is the elaboration of ribonucleic acid and through it the implementation of the synthesis of cytoplasmic proteins. The system is intensely active in cancer cells well situated for obtaining nutriment from the stroma, and potentially very active in cells in the interior of cancer cords, according to Caspersson and Santesson. These authors have recently devoted a large monograph (6) to the distribution of ribonucleic acid in 20 epithelial tumors. Their study included papillomas of the bladder showing various degrees of transition to malignancy, as well as 5 carcinomas of that organ. Nevertheless, an investigation of the changes in ribonucleic acid and heterochromatin in the course of carcinogenesis in the epidermal cells of mice painted with a solution of methylcholanthrene in benzene should be of value because this same tissue has been studied for changes in chemical composition and various cytological features (8), including chromosome size (1).

As a detailed discussion of the role of heterochromatin and ribonucleic acid in cell physiology may be found in the paper of Caspersson and Santesson (6) a few statements here will suffice. The heterochromatin, as distinguished from the euchromatin, or typical gene-bearing part of the chromosomes, is apparently concerned in nucleic acid metabolism, and generally remains condensed and definitely basophilic in the resting nucleus. Certain portions of the heterochromatin seem to be engaged chiefly in the production of plasmosomal material, such as simpler basic proteins and ribonucleic acid. According to the work of Caspersson and his collaborator, translocation of the plasmosomal material to the nuclear membrane is followed by formation at the latter organelle of cytoplasmic ribonucleic acid, which is somehow concerned in the elaboration of cytoplasmic proteins. In rapidly growing cells, and in those engaged in the synthesis of considerable quantities of protein for secretion, a high concentration of ribonucleic acid in the cytoplasm is made evident by great basophilia and notable absorption of ultraviolet light of certain wavelengths. Caspersson and Santesson suggest that in cancer cells the heterochromatin has an increased activity, perhaps because it has increased in quantity.

Theoretical significance is immediately attached to the possible role of heterochromatin in malignancy because of the demonstration of Schultz (16) that certain developmental abnormalities in *Drosophila* are related to heterochromatin changes and because of the suggestion (11) that "heterochromatinization" of various genes and chromosome regions in embryonic tissues might be a means of differentiation through the changed or lost genic activity it would entail. Hence it becomes of interest to determine changes in the number as well as the size of heterochromatic sections in epidermal nuclei during the process of carcinogenesis.

PROCEDURE

Material for this study was secured from the mice in which chromosomal changes were studied in experimental epidermal carcinogenesis (1). In brief, the mice used were adults of the New Buffalo or other closely inbred strains that were shaved on the back and a few days later painted with one brush stroke of 0.6 per cent methylcholanthrene in benzene. The painting was in most cases repeated 3 times weekly. The control mice were not painted at all, or were treated with benzene alone. At intervals 2, 3, or 4 mice that had undergone a certain number of treatments were killed with chloroform, and strips of the skin of the upper back were fixed by 2 methods.

* Treatment of the animals and preparation of the acetocarmine slides were carried out at The Barnard Free Skin and Cancer Hospital, St. Louis, while the ribonuclease-pyronin work was done at the University of Pennsylvania.

** Fellow of The International Cancer Research Foundation.

Skin fixed in Carnoy's alcohol acetic acid, 3:1, was stained with acetocarmine in squash preparations. By this means whole, unsectioned nuclei were flattened out for examination. In a preliminary study, camera lucida drawings under oil immersion and at a table magnification of 3,000 times were made of some 10 representative resting nuclei of the epidemis of each specimen; plasmosomes were outlined and all segments of heterochromatin (*i.e.*, condensed and heavily stained portions of chromatin) were drawn in solidly. The plasmosomes were analyzed as to probable initial number of units; each distinct lobulation was considered to represent one unit plasmosome. The segments of heterochromatin, including the large ones that contributed to the formation of the plasmosomes, were counted and their size noted. Included in this study were epidermises of a late embryo and a 3 day old male of albino stock mice, as well as primary methylcholanthrene epidermal carcinomas and hyperplastic epidermis near the cancers. A more thorough study was made of 30 selected specimens of control, hyperplastic, and cancerous epidermis; 50 resting nuclei of each specimen were analyzed at random for number of unit plasosomes, number and general size of heterochromatic segments, and nuclear volume, which was determined according to a method previously described (2). Although spinous and basal cells could not be separated with certainty in the acetocarmine preparations, the resting nuclei were studied in regions containing mitotic figures. No drawings were made in this final study.

Since the ribonucleic acid content was to be compared through the intensity of staining with a basic dye, it was necessary first of all to determine whether the several basophilic structures of the skin possessed basophilia by virtue of ribonucleic acid. A modification of Brachet's method (3) was used to this end. Nine slides of skin from various control and methylcholanthrene-treated animals were run through xylol and graded alcohols to water and then were placed in McIlvaine's citric acid disodium phosphate buffer of pH 7.0 containing 0.2 mgm. ribonuclease[1] per cc. Nine control slides of the same stages were placed in the buffer solution without the ribonuclease. The dishes containing the sets of control and experimental slides were kept side by side in the same water bath at 50°C.±3° for 2 hours. After incubation, both groups of slides had the media replaced once by distilled water. Then the control slides were interspersed among the experimental slides in a single dish for staining with Unna's carbol pyronin methyl green solution at 40°C. for 10 minutes. The stain was poured out and the slides were flooded with the following fluids: distilled water once, 50 per cent alcohol once, 95 per cent alcohol once, absolute alcohol twice, and xylol once. The slides were then mounted in balsam. It was found that the ribonuclease eliminated the affinity of the epidermal cytoplasm and the plasmosomes for the basic dye, pyronin, while it did not affect the basophilia of the keratin, the striated muscle fibers, the forming hair shafts, or the mast cell granules. Since the keratin and muscle fibers were stained moderately, it became possible for the intensity of their stain to be used as a standard of reference for the more variable staining capacity of the epidermal cytoplasm in slides not treated with ribonuclease. Seventy other slides were stained in 4 batches without preliminary incubation or treatment with ribonuclease.

For aid in assessing the intensity of the stain a series of comparator tubes was set up with varying concentrations of the stain. From a concentrated alcoholic solution of the stain, 10, 20, 30, 40, 60, 80, 100, 130, 160, and 215 drops were placed in 10 vials and then alcohol was added to bring the total quantity of each up to that of the last. The change in deepness of color from one concentration to the next was just discernible to the eye. The vials were placed by the microscope and given a background and illumination closely equivalent to those of the microscope field.

In a section on each slide, the extremes and average of the staining intensity were evaluated for the basal cell cytoplasm and spinous cell cytoplasm of the epidermis, for the striated muscle fibers, for the keratin, and, as a check on the latter two, for the forming hair shafts and the mast cell granules. Ratios of average staining intensity (S. I.) were then determined separately for the basal cells and the spinous cells by means of this formula:

$$\text{Ratio of S. I.} = \frac{\text{S. I. of Epidermal cytoplasm}}{\text{S. I. of Muscle fibers} + \text{S. I. of Keratin}}$$

The ratio of staining intensity thus obtained can be used as an index of the relative concentration of ribonucleic acid in the epidermal cytoplasm, subject to the specificity of ribonuclease and certain other conditions discussed later.

All observations on the intensity of stain in the sectioned tissue were made within 1 week after the slides were stained.

OBSERVATIONS

The results of the ribonucleic acid study will be described first. The ratios of staining intensity for normal control skin, for benzene-painted control skin, and for methylcholanthrene-treated skin are given in Table I. The benzene-painted controls did not display as definite an increase in the ratio as did the methylcho-

[1] I am indebted to Dr. M. Kunitz, of The Rockefeller Institute for Medical Research, Princeton, New Jersey, for the sample of crystalline ribonuclease.

TABLE I: RATIOS OF AVERAGE INTENSITY OF PYRONIN STAIN AS INDICES OF RIBONUCLEIC ACID CONTENT IN EPIDERMAL CYTOPLASM

	BASAL	SPINOUS
	No Treatment	
	0.28	0.17
	0.43	0.38
Mean	0.36	0.28
	1 Benzene 1 Day	
	0.18	0.18
	0.50	0.38
	0.57	0.57
	0.71	0.71
Mean	0.49	0.46
	1 Benzene 3 Days	
	0.27	0.27
	0.29	0.21
Mean	0.28	0.24
	3 Benzene 10 Days	
	0.36	0.29
	0.37	0.42
	0.45	0.45
	0.50	0.36
	0.69	0.62
Mean	0.47	0.43
	1 MCA ½ Day	
	0.23	0.23
	1.11	1.11
	1.13	1.00
	1.47	1.37
Mean	0.99	0.93
	1 MCA 1 Day	
	0.65	0.40
	0.69	0.69
	0.81	0.43
	0.84	0.48
Mean	0.75	0.50
	1 MCA 2 Days	
	0.40	0.19
	0.45	0.30
	0.61	0.30
	0.75	0.69
Mean	0.55	0.37
	1 MCA 3 Days	
	0.80	0.47
	1.09	0.73
	1.30	0.60
Mean	1.06	0.60

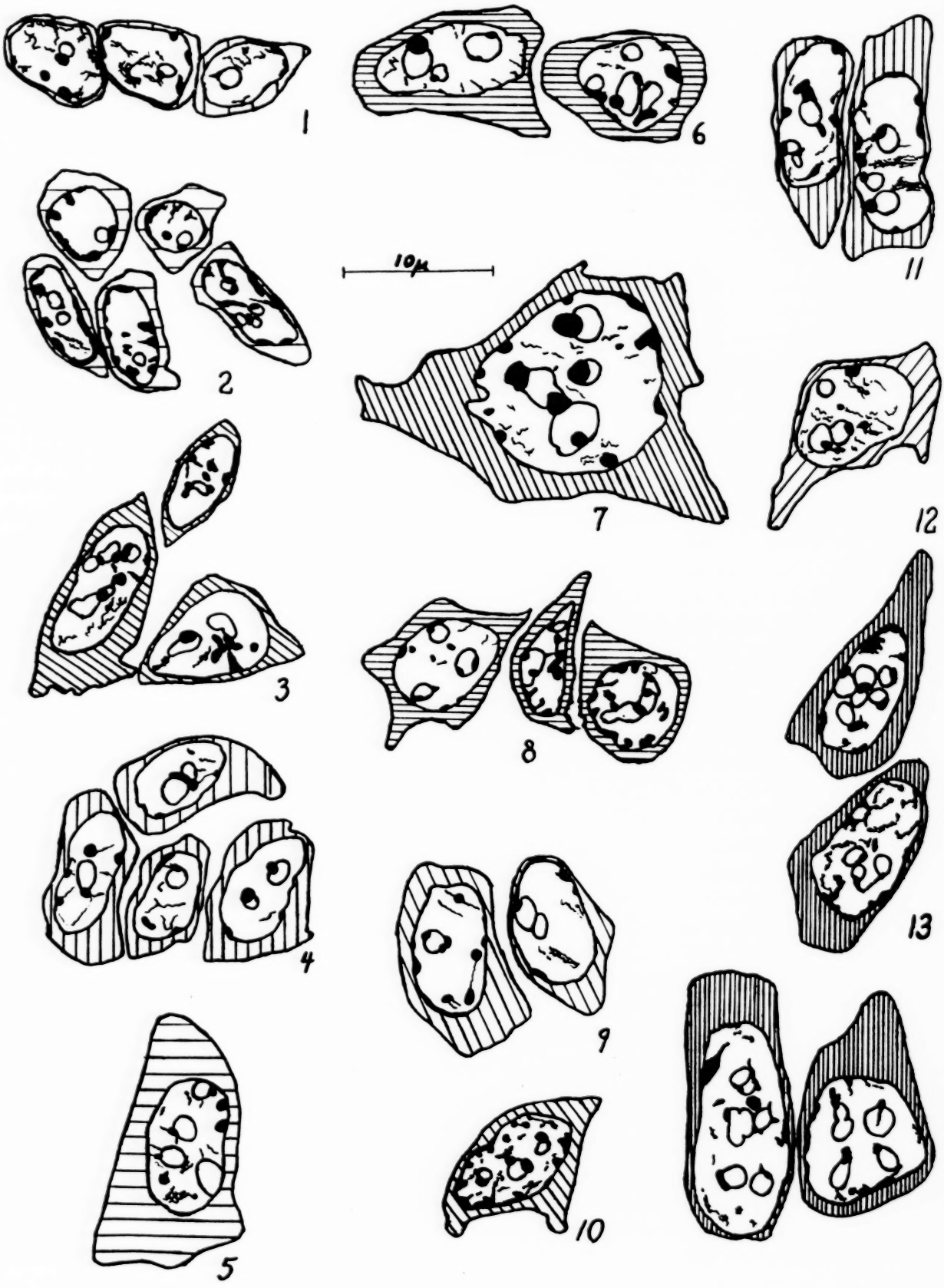
	BASAL	SPINOUS
	1 MCA 10 Days	
	0.74	0.84
	0.86	0.86
	0.88	0.69
	1.00	0.67
	1.18	1.00
	1.23	0.75
	1.24	1.12
	1.36	1.14
Mean	1.06	0.88
	2 MCA 10 Days	
	0.64	0.64
	0.69	0.69
	0.76	0.57
	0.80	0.80
	1.00	0.69
	1.15	0.85
	1.33	0.84
Mean	0.91	0.73
	3 MCA 10 Days	
	0.64	0.50
	0.65	0.28
	0.71	0.59
	0.74	0.74
	0.75	0.50
	0.89	0.50
	0.89	0.67
	0.96	0.74
	1.07	0.60
	1.11	0.67
	1.22	0.61
	1.49	0.65
	1.60	1.10
	1.61	1.00
	2.00	1.50
Mean	1.09	0.70
	6 MCA 20 Days	
	0.60	0.60
	0.64	0.64
	0.88	0.69
	1.00	0.53
	1.10	1.10
	1.40	0.80
Mean	0.79	0.73
	13 MCA 29 Days	
	0.55	0.36
	0.60	0.60
	0.63	0.63
	0.69	0.69
	0.73	0.60
	0.90	0.80
	1.36	0.86
Mean	0.78	0.65

BASAL	SPINOUS	EPIDERMAL CARCINOMA
25 MCA 57 Days		(MCA) Transplant
0.31	0.19	1.5-2.0
0.31	0.31	
0.53	0.41	
0.75	0.75	
1.00	0.89	
1.19	1.00	
Mean 0.68	0.59	

lanthrene-treated skins. There was an initial rise one-half day after the application of methylcholanthrene that was followed by a drop the first and second days after application. By the third day recovery had been made to the previous high value. The maximum ratio was maintained for at least a week, and then there seemed to occur a slow drop to another minimum at 57 days. In the one cancer studied the ratio was found to be rather high again, but this value must be accepted with the reservations discussed later. It is recalled that cancer cells do have, at least potentially, considerable quantities of cytoplasmic ribonucleic acid (6). Figs. 1 to 13 are from camera lucida drawings of individual cells of this sectioned and stained material.

The study of resting nuclei in the acetocarmine preparations revealed considerable alterations in heterochromatin and plasmosomes during carcinogenesis. These changes, together with those in nuclear volume that accompanied them, are presented in Table II. Following are descriptions of the nuclei in the various stages. It should be pointed out that the practice was followed of selecting for examination in most of the stages of carcinogenesis those 2 specimens that had proved to have the highest and the lowest frequencies of metaphases with enlarged chromosomes (1). Figs. 14 to 43 represent nuclei of normal and hyperplastic epidermises, while Figs. 44 to 51 represent nuclei of the carcinomas.

The epidermal nuclei of the late embryo, the 3 day old mouse, and the 2 untreated adult control mice were very similar. The nuclei averaged slightly over 300 cubic microns in volume and had a maximum of 4 plasmosomes, which did not differ appreciably in size from one age to another. There were from 18 to about 38, with an average of 24 or 25, segments of heterochromatin visible in each nucleus. The variability in the number of heterochromatic elements arose in part from the difficulty of distinguishing small sections of heterochromatin from chance knots of euchromatin; the distinction at small sizes was arbitrary. Moreover, overlapping or apparent fusion of segments of heterochromatin in the resting nucleus reduced the number of segments counted. Early in the prophase of mitosis the euchromatin begins to assume its heavy nucleic acid charge, and examination of such nuclei doubtless led to erroneously high estimates of the number of



FIGS. 1-13

TABLE II: NUMBERS OF HETEROCHROMATIC ELEMENTS AND PLASMOSOMES IN NUCLEI OF VARIOUS VOLUMES IN NORMAL, HYPERPLASTIC, AND CANCEROUS EPIDERMIS

Mouse No.	Treatment *	Resting nuclei			Plasmosome number	Heterochromatic segments: mean and extreme numbers
		Class	No.	Volume: Mean and extremes μ^3		
Fetus	None	I	50	222—322—503	2 to 4	18—24.8—38
11	None	I	50	132—304—552	1 " 4	18—24.4—36
12	None	I	50	193—318—649	1 " 4	18—24.0—40
59	B1—1	I	50	185—294—470	2 " 4	11—21.3—31
13	B1—3	I	50	155—330—641	1 " 4	14—21.6—31
15	B3—10	I	50	178—306—521	1 " 4	15—20.9—27
54	M1—½	I	50	153—291—431	1 " 4	15—20.0—29
55	M1—½	I	50	126—278—718	2 " 4	14—20.0—26
56	M1—1	I	50	164—463—1,000	1 " 4	16—27.9—40
57	M1—1	I	49	204—369—823	1 " 4	14—22.9—39
		I+	1	693	4 or 5	46
49	M1—2	I	48	236—572—918	1 to 4	18—27.8—44
		II	2	1,240—1,575—1,910	7, 8	60—63.5—67
50	M1—2	I	42	348—710—1,180	1 to 4	21—30.9—44
		I+	1	508	5	37
		II	7	988—1,118—1,360	4, 4+	42—49.0—62
7	M1—3	I	32	298—616—1,160	1 to 4	20—25.7—35
		I+	1	668	5	34
		II	11	708—1,031—1,470	3 to 8	37—48.6—58
		II+	2	1,410—1,435—1,460	9, 10	53—58.0—63
		III	1	1,630	2	88
		IV	3	3,550—4,340—5,200	9 to 16	88—110.7—140
8	M1—3	I	31	309—696—1,230	1 " 4	19—28.7—38
		II	12	780—1,183—1,940	4 " 8	42—49.4—60
		II+	2	1,300—1,430—1,560	10	60
		III	5	1,750—2,170—2,780	6 to 15	64—83.0—97
19	M1—10	I	50	260—429—816	1 " 4	13—19.7—26
18	M1—10	I	38	282—444—850	1 " 4	18—25.5—40
		I+	1	356	6	39
		II	6	597—954—1,440	2 to 8	42—50.7—66
		II+	1	906	10	54
		III	4	1,070—1,170—1,260	10 to 16	83—91.3—104
27	M3—10	I	47	324—501—783	1 " 4	22—29.9—44
		II	3	709—839—1,080	6 " 8	43—47.3—52
47	M3—10	I	29	477—845—1,340	2 " 4	20—28.4—38
		II	14	1,190—1,825—2,980	3 " 8	37—51.9—67
		II+	1	1,980	11	56
		III	6	1,960—2,470—3,330	8 to 14	63—82.8—114

(*Table continued on page 743*)

DESCRIPTION OF FIGURES 1 TO 13

FIGS. 1 to 13.—Semidiagrammatic representations of epidermal cells in sectioned Helly-fixed material stained with pyronin methyl green, and based on camera lucida drawings at a magnification of 2,393 times. The closeness of spacing of the lines in the cytoplasm is proportional to the concentration of ribonucleic acid. The intercellular bridges have been omitted. Within the nuclei, the solid black material represents chromatin, the spheroids plasmosomes. In each epidermal figure the horny layer of the epidermis lay toward the top of the page.

FIG. 1.—Normal; 3 basal cells, mouse 12.

FIG. 2.—Control treated 3 times with benzene over 10 days; 3 basal and 2 spinous cells, mouse 14.

FIG. 3.—One-half day after 1 painting with methylcholanthrene in benzene; 2 basal cells and 1 spinous, mouse 55.

FIG. 4.—One day after 1 treatment with methylcholanthrene; 3 basal cells, 1 spinous, mouse 57.

FIG. 5.—Two days after 1 methylcholanthrene painting; basal cell, mouse 50.

FIG. 6.—Three days after 1 methylcholanthrene painting; 2 basal cells, mouse 8.

FIG. 7.—Ten days, 3 methylcholanthrene paintings; a very large spinous cell, mouse 47.

FIG. 8.—Ten days, 3 methylcholanthrene paintings; 3 basal cells, mouse 47.

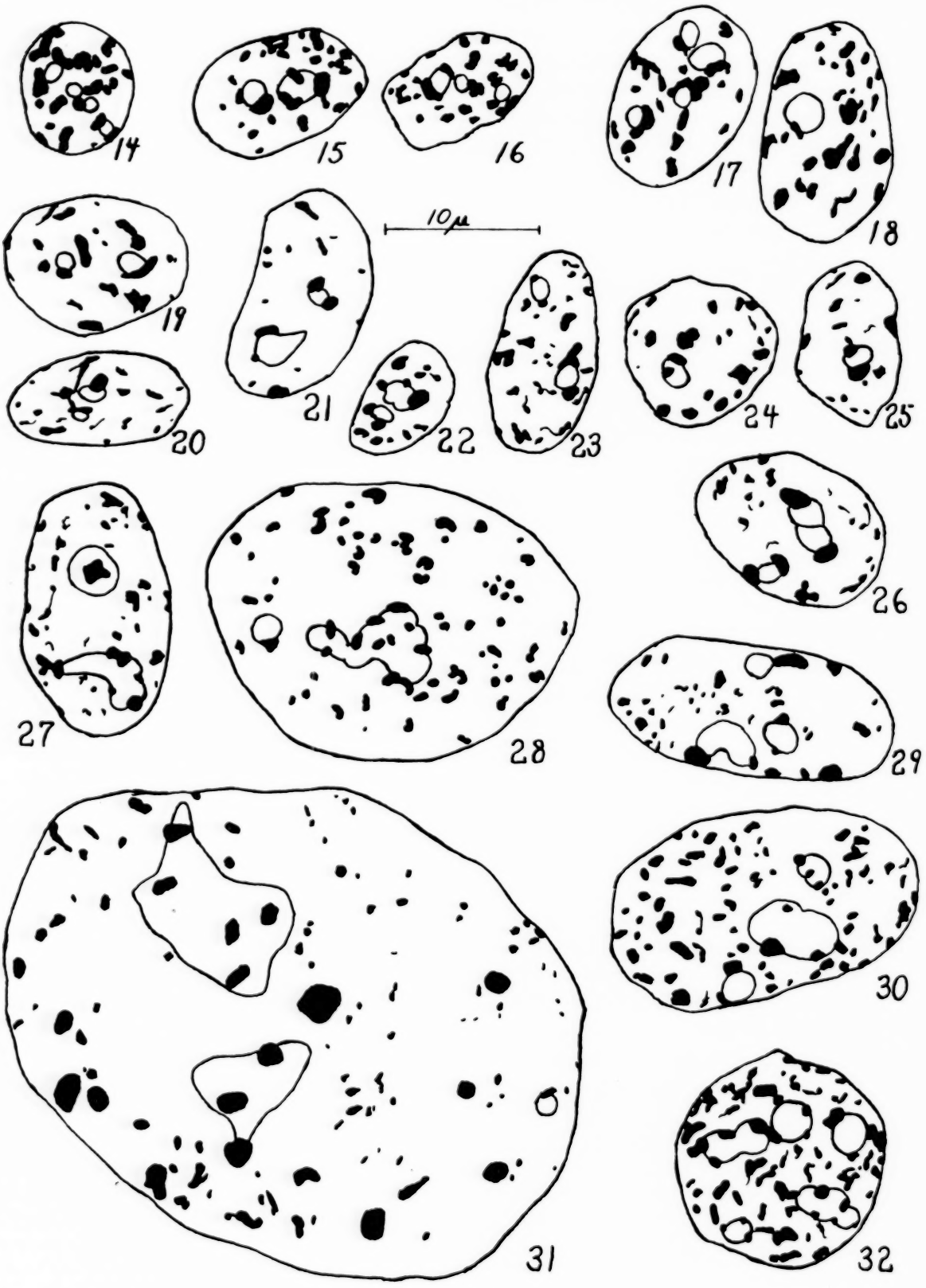
FIG. 9.—Twenty days, 6 methylcholanthrene paintings; 2 spinous cells, mouse 31.

FIG. 10.—Twenty days, 6 methylcholanthrene paintings; basal cell, mouse 33.

FIG. 11.—Twenty-nine days, 13 methylcholanthrene paintings; 2 basal cells, mouse 35.

FIG. 12.—Fifty-seven days, 25 methylcholanthrene paintings; basal cell, mouse 40.

FIG. 13.—Transplant of epidermal carcinoma; 4 cells, mouse 25. The lines in the cytoplasm are probably too close together (see text).



FIGS. 14-32

TABLE II—(*continued*)

Mouse No.	Treatment *	Resting nuclei: Class	No.	Volume: Mean and extremes μ^3	Plasmosome number	Heterochromatic segments: mean and extreme numbers
33	M6—20	I	45	268—449—742	2 " 4	20—27.8—42
		I+	1	555	5	33
		II	4	642—672—721	7 to 8	40—52.5—66
31	M6—20	I	40	260—399—702	2 " 4	20—27.9—36
		II	10	635—777—1,040	2 " 8	40—51.9—63
35	M13—29	I	48	301—476—728	1 " 4	19—28.4—40
		II	2	820—854—888	7, 8	56—57.5—59
36	M13—29	I	29	287—661—1,280	1 to 4	19—28.5—40
		II	17	768—1,145—1,480	5 " 8	43—52.7—66
		II+	1	1,630	9	61
		III	3	1,920—2,300—2,840	9 to 16	69—85.0—105
41	M25—57	I	50	222—423—690	1 " 4	16—23.5—35
38	M25—57	I	44	354—520—898	1 " 4	18—28.4—39
		II	6	869—1,046—1,440	4 " 8	47—53.5—60
42	M33—86	I	39	360—604—973	1 " 4	26—34.0—48
		II	7	801—1,242—1,500	4 " 8	58—72.1—90
		II+	2	1,140—1,400—1,660	9, 10	63—71.5—80
		III	2	1,870—1,935—2,000	11, 15	72—92.0—112
	CARCINOMAS					
42	M33—86	I	14	366—656—1,160	2 to 4	19—25.6—33
		II	29	641—1,411—2,290	3 " 8	34—49.7—66
		II+	3	1,380—1,740—2,200	9 " 12	57—60.3—63
		III	4	1,930—2,120—2,460	4 " 12	71—81.8—98
44	M36—169	I	18	311—630—1,090	2 " 4	19—27.8—37
		II	17	656—1,210—1,830	4 " 8	32—49.9—61
		II+	4	1,200—1,430—1,600	9 " 12	56—71.5—81
		III	10	1,060—1,720—2,550	8 " 14	64—88.9—113
		III+	1	2,360	20	136
5 (Tumor 1)	M5—108	I	24	227—393—616	2 to 4	18—23.5—32
		I+	3	568—593—618	5	24—31.0—38
		II	18	533—733—1,240	6 to 8	36—46.4—55
		II+	5	732—929—1,230	9 " 13	51—61.4—72
5 (Tumor 2)	M5—108	I	15	244—516—749	1 " 4	19—25.7—35
		I+	2	533—539—545	5, 6	31—32.0—33
		II	19	455—1,166—2,110	2 to 8	40—48.0—58
		II+	1	1,450	11	70
		III	10	1,980—2,425—2,870	4 to 14	70—85.6—102
		III+	1	2,210	19	125
		IV	2	4,410—4,800—5,190	11, 16	128—157.0—186

* "B1—3" indicates 1 treatment with benzene over 3 days, while "M1—½" signifies 1 painting with methylcholanthrene one-half day before. Other symbols are in accordance.

DESCRIPTION OF FIGURES 14 TO 32

FIGS. 14 to 51.—Camera lucida drawings, made to a magnification of 2,393 times, of whole nuclei in acetocarmine preparations of normal, hyperplastic, and cancerous epidermis. Heterochromatin is drawn in solidly and plasmosomes are outlined.

FIGS. 14 to 16.—Normal epidermis, mouse 11; class I nuclei with 25, 31, and 27 heterochromatic segments respectively.

FIGS. 17, 18.—Normal epidermis, mouse 12; class I nuclei with 25 and 33 heterochromatic segments.

FIGS. 19, 20.—One day after 1 benzene painting, mouse 59; class I nuclei, both with 21 heterochromatic segments.

FIGS. 21-23.—Ten days, 3 benzene paintings, mouse 15; class I nuclei with 18, 14, and 34 heterochromatic segments respectively.

FIGS. 24, 25.—One-half day, 1 methylcholanthrene painting, mouse 55; class I nuclei with 22 and 18 segments of heterochromatin.

FIG. 26.—One day, 1 methylcholanthrene painting, mouse 57; class I nucleus with 27 heterochromatic segments.

FIG. 27.—Two days, 1 methylcholanthrene painting, mouse 50; class I nucleus with 34 heterochromatic segments and probably 4 unit plasmosomes.

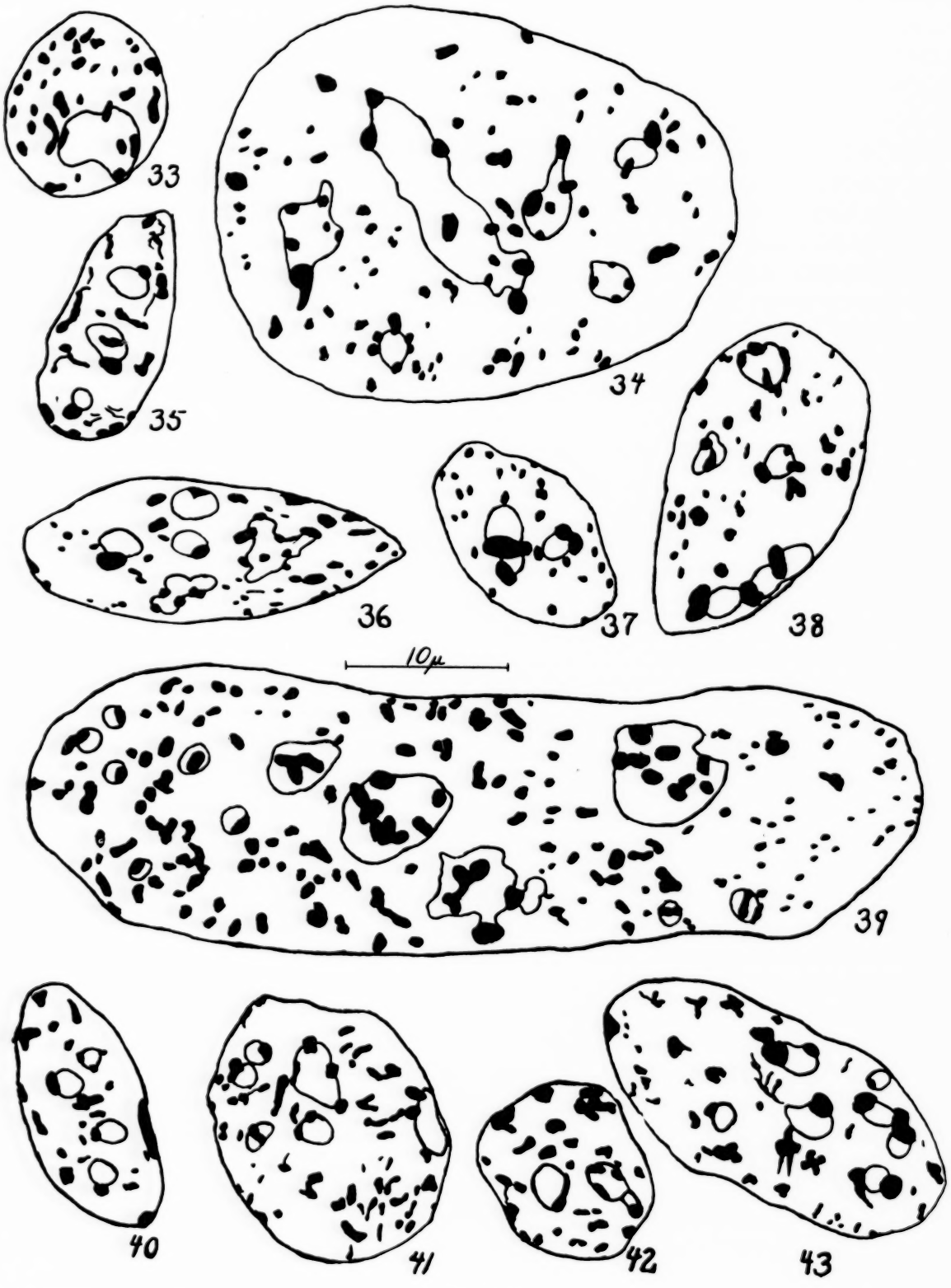
FIG. 28.—Two days, 1 methylcholanthrene painting, mouse 49; class II nucleus with 60 heterochromatic segments and probably 8 unit plasmosomes.

FIG. 29.—Three days, 1 methylcholanthrene painting, mouse 9; class I nucleus with 30-odd heterochromatic segments and 4 unit plasmosomes.

FIG. 30.—Three days, 1 methylcholanthrene painting, mouse 9; class II nucleus with 65 heterochromatic segments.

FIG. 31.—Three days, 1 methylcholanthrene painting, mouse 7; class III nucleus with about 103 heterochromatic segments and several large compound plasmosomes.

FIG. 32.—Ten days, 2 methylcholanthrene paintings, mouse 22; class II nucleus with 57 heterochromatic segments and 8 unit plasmosomes.



FIGS. 33-43

heterochromatic segments. These conditions of uncertainty held in the examination of other stages as well as the normal controls.

Application of benzene alone caused characteristic changes in the appearance of epidermal nuclei. Although the nuclei were of the same size as those of the untreated control and the plasmosomes had changed neither in number nor in size, the nuclei after benzene treatment had an empty, watery appearance, and some of the now approximately 21 segments of heterochromatin exhibited a tendency to string out in long filaments. Here again it was difficult to draw the distinction between heterochromatin and euchromatin. The epidermal nuclei looked the same after 10 days and 3 paintings as after 1 or 3 days and 1 painting.

The characters of the benzene-treated nuclei extended to those of epidermis taken one-half day after treatment with methylcholanthrene in benzene, although all later stages of methylcholanthrene treatment were different. After one-half day the nuclei had not enlarged. They contained an average of 20 often filamentous segments of heterochromatin and had a maximum of 4 plasmosomes that were of the original small size. However, the plasmosomes in the acetocarmine preparations of this stage were nearly unstained. Although the staining capacity was little decreased from the low staining capacity of plasmosomes of benzene-treated epidermis, it did seem to be somewhat lower than that in untreated controls and considerably lower than that in epidermis treated longer with methylcholanthrene.

One day after 1 painting with methylcholanthrene in benzene, the epidermal nuclei were enlarged to an average of 369 and 463 cubic microns, instead of the former 300. In the larger nuclei the plasmosomes were definitely of a larger size. In only 1 of the 100 nuclei examined were there more than 4 plasmosomes. The nucleus concerned had 5 plasmosomes, a volume near 700 cubic microns, and 46 visible heterochromatic elements. The number of heterochromatic segments in the other nuclei averaged about 23 and 28 in the 2 specimens.

Two days after 1 application of methylcholanthrene the nuclei were sufficiently variable in size and other characters to be grouped into 2 classes. About 90 per cent of the nuclei were in class I; they had an average volume of 600 or 700 cubic microns, which represented a doubling of the original volume; the plasmosomes were usually enlarged and numbered from 1 to 4, and the average numbers of heterochromatic segments were 28 and 31. The nuclei of class II were about twice as large as those of class I, had up to 8 plasmosomes, and seemed to contain twice as many bits of heterochromatin as the class I nuclei. The inference is inescapable that the nuclei of class II, as well as those of higher classes arising in later stages, contained a greater number of chromosome strands. In assigning nuclei to particular classes, the practice was followed of giving greater weight to the plasmosome number or the number of heterochromatic segments, whichever was relatively greater, rather than to the nuclear volume.

By the third day after 1 application of methylcholanthrene in benzene there was almost as much nuclear variability as appeared in any later stage or in the cancers. Nuclei of all classes through class IV were present. As in all stages up to the carcinomas, class I was in the majority and in this stage made up 60 per cent of the total. The nuclei of this class had not increased particularly in volume from the second to the third day; indeed, the average nuclear volumes of the several classes were well established by the third day, and they later underwent no notable increases, even in the cancers. Class I nuclei averaged about 600 to 700 cubic microns, class II nuclei 1,000 to 1,200 cubic microns, class III nuclei about 2,200 cubic microns, and

DESCRIPTION OF FIGURES 33 TO 43

FIG. 33.—Ten days, 3 methylcholanthrene paintings, mouse 47; class I nucleus with 31 heterochromatic segments.

FIG. 34.—Ten days, 3 methylcholanthrene paintings, mouse 47; class III nucleus with about 111 heterochromatic segments and perhaps up to 16 unit plasmosomes.

FIG. 35.—Twenty days, 6 methylcholanthrene paintings, mouse 31; class I nucleus with 25 heterochromatic segments and 3 or 4 unit plasmosomes.

FIG. 36.—Twenty days, 6 methylcholanthrene paintings, mouse 31; class II nucleus with 52 heterochromatic segments and 5 plasmosomes, 2 of them compound.

FIG. 37.—Twenty-nine days, 13 methylcholanthrene paintings, mouse 35; class I nucleus with 30 heterochromatic segments and 3 plasmosomes.

FIG. 38.—Twenty-nine days, 13 paintings with methylcholanthrene, mouse 35; class II nucleus with 53 heterochromatic segments and at least 6 unit plasmosomes.

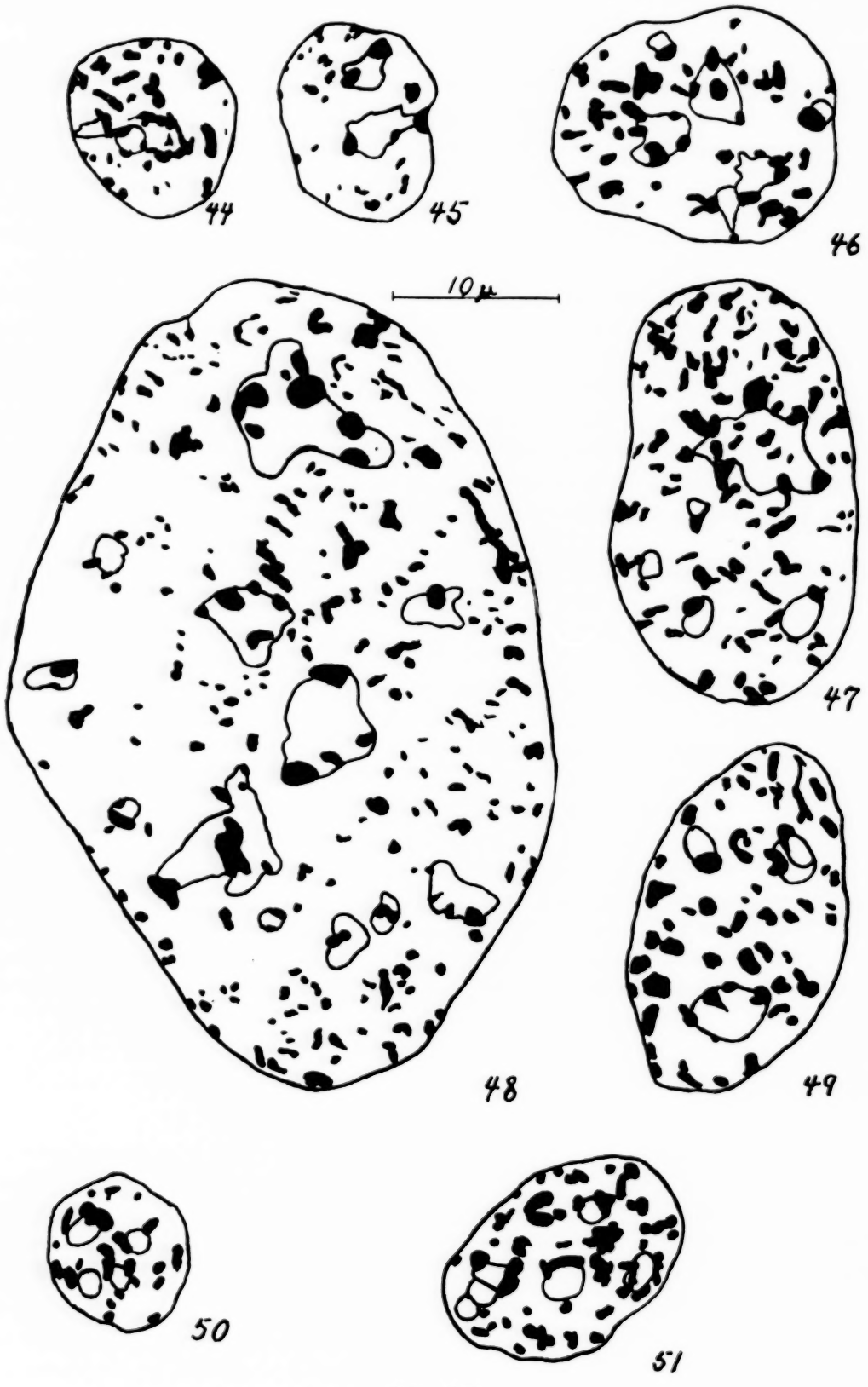
FIG. 39.—Twenty-nine days, 13 methylcholanthrene paintings, mouse 36; class IV nucleus with 190 heterochromatic segments and 8 simple and 4 greatly compound plasmosomes.

FIG. 40.—Fifty-seven days, 25 methylcholanthrene paintings, mouse 39; class I nucleus with 26 heterochromatic segments and 4 plasmosomes.

FIG. 41.—Fifty-seven days, 25 methylcholanthrene paintings, mouse 39; class II nucleus with 58 heterochromatic segments and about 8 unit plasmosomes.

FIG. 42.—Ninety-four days, 36 methylcholanthrene paintings, mouse 43; class I nucleus with 34 heterochromatic segments and at least 3 unit plasmosomes.

FIG. 43.—Ninety-four days, 36 methylcholanthrene paintings, mouse 43; class II nucleus with 56 heterochromatic segments and perhaps 8 unit plasmosomes.



FIGS. 44-51

class IV about 4,300 cubic microns. The average numbers of heterochromatic elements for these classes were 26 to 29, 49, 83, and 111 respectively. Some of the spinous nuclei of this stage contained large vacuoles.

Epidermis taken 10 days after 1 treatment with methylcholanthrene was similar to that treated twice over the same period. At this stage, in mouse 19, there was an example of the nearly complete absence of a response to methylcholanthrene. The epidermis closely resembled that of animals treated with benzene only. The heterochromatic segments averaged 19.7 in number and were somewhat filamentous, the plasmosomes were small, and the nuclei, which were all in class I, had the appearance of being partly empty, since there was little euchromatic granularity. There were differences between this epidermis and that treated with benzene only: the nuclear volume, for instance, was greater in the carcinogen-treated epidermis, and the nucleoli were slightly larger and perhaps more heavily staining. The other skin studied at this stage exhibited a more pronounced response, as its nuclei were in three classes with the expected number of heterochromatic segments.

After 3 treatments with methylcholanthrene over 10 days, nuclei of all classes were again relatively large. The average numbers of heterochromatic sections were 28 and 30 for class I, and 47 and 52 for class II.

Later stages, which included 6 treatments with the carcinogen over 20 days, 13 treatments over 29 days, 25 treatments over 57 days, and 33 over 86 days, exhibited no great digressions from the trends already established. Occasional skins were found to react little to methylcholanthrene, but at every stage nuclei of class II, which seem to possess signal importance in carcinogenesis, were present.

Nuclei of class II were especially well represented in the 4 carcinomas studied. Containing about 50 segments of heterochromatin and up to 8 unit plasmosomes, the nuclei of class II usually made up the most numerous class. The preponderance of nuclei of higher classes in cancers constituted the one distinctive nuclear difference between epidermis undergoing methylcholanthrene hyperplasia and the carcinomas derived from such epidermis. That the class I nuclei in the cancers had been affected by the carcinogen, however, was to be seen in the enlargement of their plasmosomes.

The second tumor of mouse 5 and the cancers of mice 42 and 44 presented roughly the same average nuclear pictures: class I nuclei of about 600 cubic microns, with 2 to 4 plasmosomes and 26 segments of heterochromatin; class II nuclei of about 1,200 cubic microns, with 8 unit plasmosomes and 49 heterochromatic elements; class III nuclei of about 2,100 cubic microns, with about 14 unit plasmosomes and 86 heterochromatic elements; and class IV nuclei (in the second tumor of mouse 5) of about 4,800 cubic microns, with numerous plasmosomes and 157 pieces of heterochromatin. The first tumor of mouse 5 was distinctive in the smallness of its nuclei, which extended through both classes I and II. The nuclei of class I averaged 393 cubic microns in volume and contained 2 to 4 plasmosomes and an average of 23.5 segments of heterochromatin. The nuclei of class II had a mean volume of 733 cubic microns and held 6 to 8 plasmosomes and an average of 46.4 segments of heterochromatin. The difference in size of nuclei between the 2 cancers of mouse 5 was readily evident in sectioned material as well as in acetocarmine preparations.

In the cancers, especially the larger nuclei often contained rather large masses of heterochromatin. These could very well have been large as the result of fusion of smaller segments, and in some cases they were probably fused homologous sectors of the chromonemata of multiple-stranded chromosomes. That fusion did often occur was indicated by the progressively greater decrease from integral powers of 2 times the average number of heterochromatic segments of class I nuclei as larger nuclei were studied. The possession of large masses of heterochromatin was not peculiar to cancer nuclei, however. Nuclei of higher classes in the hyperplastic epidermises also contained them, but the phenomenon may have been more pronounced in the cancers.

One final observation is to be noted. There was a

DESCRIPTION OF FIGURES 44 TO 51

FIG. 44.—Cancer, mouse 43; class I nucleus with 35 heterochromatic segments and 2 plasmosomes.

FIG. 45.—Cancer, mouse 43; class I nucleus with 29 heterochromatic segments and 2 plasmosomes.

FIG. 46.—Cancer of mouse 43; class II nucleus with 50 heterochromatic segments and 6 plasmosomes, some of them compound.

FIG. 47.—Cancer of mouse 43; class III nucleus with 100 heterochromatic segments and 4 simple and 1 large compound plasmosome.

FIG. 48.—Cancer of mouse 42 (86 days, 33 methylcholanthrene paintings); class IV or V nucleus with 244 heterochromatic segments and 12 plasmosomes, many of which are compound.

FIG. 49.—Cancer of mouse 42; class II nucleus with 57 heterochromatic segments and at least 4 unit plasmosomes.

FIG. 50.—First cancer of mouse 5 (108 days, 5 methylcholanthrene paintings); class I nucleus with 23 heterochromatic segments and 4 plasmosomes.

FIG. 51.—First cancer of mouse 5; class II nucleus with 56 heterochromatic segments and 6 plasmosomes.

good correspondence between the frequency of nuclei of classes above class I and the previously reported (1) frequency of metaphases containing enlarged chromosomes. Table III sets forth the agreement. The 2 specimens chosen for study from each stage were selected as those likely to give great discrepancies. We draw the conclusion that the nuclei of higher classes probably contained enlarged, multiple-stranded chromosomes. In the previous study no polyploid division figures with simple chromosomes were found (1). In the 4 cancers the frequencies of metaphases with enlarged chromosomes exceeded the frequencies of resting nuclei of higher classes, while in all earlier stages the opposite was true. Unless this is a matter of random error, it suggests that in the cancers the nuclei with multiple-stranded chromosomes may be relatively more viable than their counterparts in the hyperplastic epidermises.

TABLE III: COMPARISON OF THE FREQUENCIES OF METAPHASES CONTAINING ENLARGED CHROMOSOMES WITH THE FREQUENCIES OF RESTING NUCLEI ABOVE CLASS I

Stage *	Mouse No.	Metaphases with enlarged chromosomes per cent	Resting nuclei above class I, per cent
0—0	11, 12	0	0
B—1-10	59, 13, 15	0	0
M1—½	54, 55	0	0
M1—1	56	0	0
M1—1	57	0	2
M1—2	49	2?	4
M1—2	50	2	16
M1—3	7	12	36
M1—3	8	20	38
M1—10	19	0	0
M1—10	18	10	24
M3—10	27	4	6
M3—10	47	28	42
M6—20	33	4	10
M6—20	31	12	20
M13—29	35	2?	4
M13—29	36	20	42
M25—57	41	0	0
M25—57	38	5	12
M33—86	42	20	22
CARCINOMAS			
M33—86	42	80	72
M36—169	44	82	64
M5—108	5 (tumor 1)	54	52
M5—108	5 (tumor 2)	86	70

* See footnote to Table II.

DISCUSSION

Probable reasons for variability in the counts of heterochromatic segments in acetocarmine preparations have been discussed above. There were several sources of error in the estimation of relative content of ribonucleic acid in the sectioned material. The visual matching of color intensities, for example, provided an opening for considerable error. The use of only 10 points on the scale of color intensity made for crudeness. There was also variability in the washing out of the pyronin from the sections during dehydration in the alcohols. Errors arising from this latter variability were obviated to some extent, however, by a comparison of the staining intensities of epidermal cytoplasm, muscle, and keratin at points close to one another on the same section. The ratio of staining intensity presumably due to the attraction of ribonucleic acid in the epidermal cytoplasm to the intensity of "nonspecific" staining of the keratin and muscle is valid as an index of ribonucleic acid concentration only if certain conditions are met: (a) the concentrations of the acid substances responsible for the staining of the keratin and muscle must not be notably influenced by the treatment with benzene or methylcholanthrene, and their concentration should be less variable than is the degree of washing out of the stains from the sections in upgrading through alcohol; (b) the pyronin must be washed off the acid groups of keratin and muscle with about the same speed as that with which it is washed off ribonucleic acid. The second condition seems to have been met, since ratios of the intensity of stain agreed fairly well for given animals from one batch to another of the 5 stainings. It also appears that under treatment with methylcholanthrene the concentration of ribonucleic acid in the epidermal cytoplasm exhibited greater variability than did the concentrations of the substances responsible for pyronin staining in the keratin and muscle.

The nature of the supposedly acidic substances that combine loosely with pyronin in the muscle and keratin is of interest. If the substances of concern in the muscle are nucleotides, it is to be expected that pyronin should behave toward muscle as it behaves toward cytoplasm containing ribonucleic acid. Since keratin is now thought to be formed by unfolding of the coiled proteins of the cells into bundles of straight polypeptide chains (15), it may be that exposed carboxyl groups in keratin exert the attraction for pyronin. It is obvious that, should the nature of the cellular proteins change much in carcinogenesis, keratin of normal or benzene-treated epidermis might differ in affinity for pyronin from keratin of epidermal carcinomas or of epidermis undergoing methylcholanthrene-induced hyperplasia. It is for this reason, as well as because no muscle was available in the sections for comparison, that the ratio of 1.5 to 2.0 obtained for the transplanted epidermal carcinoma must be accepted with qualifications.

Although about 800 separate estimations of staining

intensity were made, there were too few determinations of the ratio of staining intensity of the epidermal cytoplasm to that of the keratin and muscle at individual stages of treatment for much statistical significance to be assigned the differences between means of any 2 stages. However, the mean of the ratios for the basal cell cytoplasm in all the controls, 0.43 ± 0.16, does differ significantly from the corresponding mean in the methylcholanthrene-treated tissues, 0.92 ± 0.35, inasmuch as the difference between the means, 0.49, is about 8 times its standard error, 0.063.

In view of the possibilities of error discussed above, what conclusions are permissible?

Treatment with benzene alone seems to cause little change in ribonucleic acid content of cytoplasm or in volume of nucleus and plasmosomes. The heterochromatin is characteristically affected, however, as a few segments of it disappear and the rest often becomes more filamentous instead of concentrated in blocks.

Methylcholanthrene applied in benzene to the skin brings about an immediate increase in ribonucleic acid in the thin envelope of cytoplasm surrounding the epidermal nuclei. This ribonucleic acid, at one-half day after treatment, may have been derived from the now nearly unstained plasmosomes that are still of normal smallness. The succeeding 2 days witness a gradual expansion of the cytoplasm and a consequent dilution of the ribonucleic acid first given out. By the third day the plasmosomes in nearly all cells have enlarged to the size characteristic in cancer and the steadily growing cytoplasm again contains ribonucleic acid in high concentration. Nuclear volume is generally increased and highly variable, and to a considerable extent the number or size of heterochromatic segments is likewise increased in correspondence with the number of plasmosomes and the nuclear volume. In later stages the extent of variability is maintained, although small nuclei seem to increase temporarily in frequency at about 2 months.

On the third day, and to a lesser extent on the second day, there have appeared the nuclei that would seem to be of great significance in carcinogenesis: nuclei of double class I volume, with double the normal number of unit plasmosomes; with double the original number of heterochromatic segments, which are not necessarily increased in size; and with chromosomes of the diploid number but of twice the usual size. These class II nuclei, earlier termed the "tumor-diploids" (2), are present in all stages until their full flowering in the cancers.

The possession of the doubled number of heterochromatic segments by the "tumor-diploid" nuclei is of significance in the interpretation of the structure of cancer chromosomes. Schultz (16) has found that heterochromatin divides more slowly than euchromatin in the polytene chromosome bundles of the nurse-cells of the fruit fly ovary. Might incomplete reproduction in the heterochromatin account for the fact that cancer chromosomes are multiple stranded? Apparently it would not, for the evidence is clear that the heterochromatic elements double in number when the chromosomes double in size in epidermal carcinogenesis of the mouse.

There seems to be an increase in euchromatic granularity through carcinogenesis, and in many of the cancer cells the segments of heterochromatin have increased in size and number. While chromosomal polyteny and polyploidy would appear sufficient to account for the changes in heterochromatin from the normal to the cancerous condition, the evidence here given does not allow the statement to be made that in carcinogenesis there has not occurred a "heterochromatinization" of some normally euchromatic genes, nor that hypertrophy or independent multiplication of some heterochromatic "genes" has not taken place. Nuclear swelling and consequently less crowding together of heterochromatic segments may account for the apparent slight but questionable increase in their number in a given class from the normal to the cancerous condition. It should be noted that the numbers of heterochromatic segments seen in class I nuclei of the small-nucleate first tumor of mouse 5 were identical with those of the normal controls. The photometric observations of Stowell (17) on Feulgen-stained sections also show that the majority of nuclei in epidermis made hyperplastic with methylcholanthrene contain no more or little more heterochromatin (as thymonucleoprotein) than do normal nuclei. The possession of enlarged plasmosomes by nuclei without increased complements of heterochromatin probably means that the synthetic activity of heterochromatin can be increased without a corresponding enlargement of the sections of heterochromatin or an increase in their number. This does not necessarily refute the suggestion of Caspersson and Santesson (6) that an increased quantity of heterochromatin might account for the larger nucleoli and greater amount of cytoplasmic ribonucleic acid in cancer cells. On the other hand, it need not support Koller's hypothesis (10) that a somatic mutation in the heterochromatin causes excess production of nucleic acids in cancer cells, especially since it is not known whether these small-nucleate cells with enlarged plasmosomes revert to the normal condition when the carcinogen is no longer applied.

Our study demonstrates that the increase in nuclear volume studied by Page (12), Pullinger (13), and Cowdry and Paletta (9) in carcinogen-treated epidermis probably results from 2 processes: (a) a doubling of the chromosome strands in some of the nuclei, with

a consequent doubling of related nuclear organelles; and (b) an increase in size in about all the nuclei, apparently independent of any increase in chromosomal nucleoprotein.

The change of ribonucleic acid in the epidermal cytoplasm is very early of considerable magnitude. Its apparent precedence in time over some of the other known changes in methylcholanthrene-treated epidermis may indicate a causal relationship in some cases. This is perhaps true in part for the cytoplasmic enlargement noted by Pullinger (13) and by Cowdry and Paletta (9), since ribonucleic acid is thought to be concerned in the synthesis of cytoplasmic proteins (6). Whether ribonucleic acid has anything to do with the progressive increase in incidence of mitosis that has been found to set in by 18 hours after treatment with methylcholanthrene and last for 37 days (14) is debatable, but the coincidence of the minimum in ribonucleic acid concentration at about 2 months with a minimum in mitotic incidence (7) is suggestive of a relationship. The general similarity of the progression of the average ratios for pyronin-staining intensity to the progression of the average frequencies of enlarged-chromosome metaphases may be of significance. However, among the animals at individual stages of treatment there was usually a poor correlation between the frequency of enlarged chromosomes and the ratio of staining intensity of the epidermal cytoplasm. Hence it may be true that the change in cytoplasmic concentration of ribonucleic acid and the formation of enlarged chromosomes are relatively unrelated products of the collision of the carcinogen with chromatin.

Stowell (17) has determined photometrically a progressive decrease in the concentration of thymonucleic acid per unit volume of epidermis from normal skin through skin painted twice with methylcholanthrene in benzene over 10 days to skin painted 9 times over 24 days. Nevertheless, according to Carruthers and Suntzeff (4, 5), the concentration of nucleoprotein phosphorus per unit weight maintains approximate constancy or even increases slightly throughout epidermal carcinogenesis. It might be possible to harmonize these observations by means of the increase in ribonucleic acid here described.

SUMMARY

Mouse epidermis painted with methylcholanthrene in benzene was studied for changes in cytoplasmic ribonucleic acid concentration by means of ribonuclease and a basic dye, and for changes in heterochromatin in whole nuclei of acetocarmine preparations.

Cytoplasmic ribonucleic acid concentration was notably increased by one-half day after treatment, was at a maximum from the third to the tenth day, and thereafter dropped to an intermediate value by the 57th day. It was high again in the one cancer studied, and it remained at normal levels in controls treated with benzene alone.

Nuclei bearing multiples of the normal number of heterochromatic segments were in evidence from the second day of treatment on through carcinogenesis and were predominant in the cancers. Such nuclei, which also contained increased numbers of plasmosomes and were relatively large, were closely paralleled in frequency by metaphases containing enlarged chromosomes. It is doubtful that there is any increase in number or size of heterochromatic segments in either hyperplasia or carcinoma induced by methylcholanthrene that is not explicable on the basis of multiple-stranded chromosomes and polyploidy.

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Alkaline Phosphatase in Mouse Skin under Methylcholanthrene Treatment*

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The undoubted importance of phosphate transfer in metabolism and of metabolic changes in carcinogenesis makes desirable a determination of changes in phosphatase activity of mouse skin treated with carcinogens. As one enzyme or one group of closely related enzymes (9) responsible for part of the total phosphatase activity, alkaline glycerophosphatase can be studied histochemically. Gomori's method (6) makes possible a close histological and cytological study of the localized activity of alkaline phosphatase in the skin.

MATERIALS AND METHODS

The mice used were the New Buffalo mice that served as material for the study of chromosomal changes in carcinogenesis of the skin by Biesele and Cowdry (2). They had been shaved on the back several days before being painted with 0.6 per cent methylcholanthrene in benzene. The painting was usually repeated 3 times a week, and groups of 2, 3, or 4 mice were killed with chloroform at $\frac{1}{2}$, 1, 2, 3, 10, 20, 29, and 57 days after the first painting. Strips of skin adjacent to those used for the study of chromosomes (2) and ribonucleic acid (1) were fixed in 80 per cent alcohol for 1 day, embedded in paraffin, and sectioned to a thickness of 6 microns. Normal and benzene-painted control skins, as well as a transplant of a methylcholanthrene skin carcinoma, were handled in the same manner.

The slides were treated for the demonstration of alkaline glycerophosphatase some 10 months later, the procedure of Gomori (6) being followed with a few modifications. The time of incubation of the sections was increased from $1\frac{1}{2}$ to 24 hours, because it had been found earlier that only pale staining occurred after incubation for the shorter time. The paraffin sections were passed through xylol and graded alcohols to water and then incubated at 38°C. in an alkaline solution composed of 2.5 parts of 2 per cent sodium glycerophosphate, 2 parts of 2 per cent sodium barbital, 1 part of 2 per cent calcium chloride, 6 parts of $M/50$ magnesium chloride, and 0.5 part of distilled water. After 24 hours the slides were rinsed in several changes of 1 per cent calcium chloride, placed for 2 minutes in 2 per cent cobalt chloride, rinsed in distilled water, covered for 1 minute by a dilute solution of ammonium sulfide, washed with tap water, dehydrated, cleared, and mounted. It should be made clear that the various solutions were poured into and out of the dish containing the slides; the latter were not transferred one by one.

Four types of control procedures were executed. For the first type, 2 representative sets of slides were treated in the same manner as were the experimental slides, except that the glycerophosphate solution in the incubation medium was replaced by distilled water. For the second type, the calcium chloride in the incubation fluid and in the rinse was replaced by distilled water. Slides of the third control type were merely rinsed in the incubation solution less than a minute; otherwise they were treated like the experimental slides. The fourth control omitted the incubation and subsequent treatment; only hydrating, dehydrating, clearing, and mounting were carried out.

OBSERVATIONS

The controls will be described first. The fourth control type, in which incubation and treatment with the various chemical solutions were omitted, yielded only completely clear, unstained sections.

The other 3 control groups gave results essentially like one another. Hence it is possible that the treatment with cobalt chloride and ammonium sulfide, not the incubation, was responsible for such stain as appeared in these controls. In the untreated skins and the benzene-painted skins practically no stain could be seen; only in the nuclei of the hair-follicle cells was there a light precipitate. Sections of methylcholanthrene-treated skins showed a definite, although not heavy, staining of the epidermal nuclei and of those elements of the skin, in general, that stained fairly heavily after full incubation. If this control staining be taken as evidence of preformed phosphate, as Moog

* This study was begun at the Barnard Free Skin and Cancer Hospital, St. Louis, and finished at the University of Pennsylvania.

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(12) believes, the conclusion may be drawn that the concentration of preformed phosphate paralleled the activity of alkaline glycerophosphatase as seen on full incubation.

Definite and progressive changes in alkaline phosphatase activity in carcinogenesis were revealed by incubation with the complete solution. Table I shows the comparative density of precipitate in the nuclei of basal and spinous cells of the epidermis and in the collagen fibers and connective tissue nuclei of the dermis. It is of interest that the papillary layer of the dermis stained less heavily than the reticular layer throughout the series.

and cytoplasm were better defined. A sharp contrast in staining, which was to be even more noticeable under methylcholanthrene treatment, had developed between the unstained papillary layer and the reticular layer. The contrast extended to the follicular cells, which were much paler where the hair follicles passed through the papillary layer.

In addition to the normal and benzene-painted skins, a control of a sort was furnished by a wound topped by a scab that happened to be on a skin treated with methylcholanthrene ½ day before fixation. Practically no alkaline phosphatase reaction to the methylcholanthrene was to be seen at this stage. The wound,

TABLE I: RELATIVE DENSITY OF PRECIPITATE IN TEST FOR ALKALINE PHOSPHATASE

The values given are the predominant values followed by the extremes

Treatment, No.	Days	Basal cell nuclei	Spinous cell nuclei	Connective tissue cell nuclei	Collagen Fibers
0	0	1+: 1+	1+: 1+	2+: 2+	1+: 1+
BENZENE					
1	1	1+: 1+	1+: 1+	2+: 2+	1+: 0, 1+
1	3	2+: 2+	1+: 1+	2+: 2+, 3+	1+: 1+
3	10	2+: 2+	1+: 1+	3+: 2+, 3+	1+: 1+
METHYLCHOLANTHRENE					
1	½	1+: 1+	1+: 1+, 2+	1+: 1+	0: 0
1	1	3+: 3+	2+: 2+	3+: 3+	2+: 2+
1	2	5+: 3+, 5+	3+: 2+, 3+	5+: 5+, 6+	4+: 3+, 6+
1	3	5+: 4+, 5+	3+: 3+	6+: 5+, 6+	5+: 4+, 6+
1	10	4+: 4+	2+: 2+, 3+	4+: 3+, 5+	4+: 3+, 4+
2	10	2+: 2+	2+: 2+	3+: 3+	3+: 3+
3	10	4+: 2+, 5+	3+: 1+, 4+	5+: 2+, 6+	5+: 1+, 6+
6	20	4+: 2+, 4+	3+: 2+, 3+	4+: 4+	5+: 4+, 6+
13	29	4+: 1+, 4+	2+: 1+, 2+	3+: 3+	4+: 4+
25	57	4+: 1+, 4+	2+: 1+, 3+	3+: 2+, 3+	4+: 3+, 5+
PAPILLOMA					
25	57	6+: 1+, 6+	3+: 1+, 5+	6+: 6+	6+: 6+
CARCINOMA					
		6+: 1+, 6+	3+: 1+, 3+	6+: 6+	6+: 6+

Sections of normal skin gave evidence of phosphatase activity in a moderate staining of the nuclei of hair-follicle cells and in nuclei of the reticular layer of the dermis, a heavy staining of the blood vessels, the sebaceous glands, and the granules of the occasional mast cells, and a light staining of the muscle fibers. The epidermal cells were very lightly stained, if at all. Examination of the control slides revealed that about half of the staining of the muscle fibers and the follicular cells occurred without complete incubation and was hence not attributable to phosphatase activity.

Three days after treatment with benzene alone there was a slight increase in the stain in parts of the skin. The basal cell nucleoli were becoming barely apparent. Three treatments with benzene over 10 days increased the reaction slightly again, and the basal cell nuclei

however, which was probably occasioned by the shaving of a few days before, was similar in its phosphatase reaction to the description given by Fell and Danielli (5) for the later stages of wound healing in rat skin. In the dermis beneath the scab there was a collar of moderately stained fibroblasts and fibers surrounding a space containing cells stained less than the collar cells but more than dermal cells elsewhere. Above the collar the epidermal cells gave evidence of moderate phosphatase activity in the nuclei, but directly beneath the center of the scab the hyperplastic epidermis was stained less deeply.

By the end of the first day after the painting with methylcholanthrene in benzene, most of the basal cells had a light nucleolar stain, and some had a heavier stain, which extended to granules of chromatin that

may have been chromosomal detritus, according to Moog (12). The spinous cells were now becoming visible, about like the basal cells 3 or 10 days after treatment with benzene alone. The connective tissue cells of the reticular layer were moderately stained, as were the forming collagen fibers.

By the second and third days the maxima in the reactions of nearly all elements, exceeded only in the papilloma and carcinoma, were reached. The most heavily stained epidermal basal cells contained very black nucleoli and granules of chromatin, and their cytoplasm was moderately stained.

In all later stages the reaction was variable, but followed a definite pattern. In regions of the skin in which the hair follicles had been destroyed, the reticular layer of the dermis gave little evidence of present phosphatase activity. Above such regions the epidermis was most highly hyperplastic and the histochemical test for alkaline glycerophosphatase nearly negative. In regions of less definite or slower histological reaction to the carcinogen, where the reticular layer, containing fibroblasts and mast cells, was still evident by its fairly heavy staining, the epidermal cells also had fair phosphatase activity. The closer the phosphatase-positive dermal structures were to the basal layer of the epidermis, the more strongly positive were the cells of the latter, especially in their nuclei. This variability is not well expressed in Table I.

The papilloma and transplanted epidermal carcinoma examined proved to be very similar in point of localization and degree of phosphatase activity. The epidermal cells close to the nutrient stroma were very heavily stained, and this was true of the cytoplasm as well as the nucleoli and granular chromatin. The suprabasal cells became increasingly more lightly stained, the greater their distance from the stroma. Near foci of keratinization, even the nucleoli seemed to be almost devoid of the enzyme. The stroma, apparently containing connective tissue cells and collagen fibers, was itself intensely positive for alkaline phosphatase.

DISCUSSION

The long time of incubation employed in this study gave positive values for alkaline phosphatase to some cell types and tissues that under shorter incubation would have been recorded as negative. Similarly, Wolf, Kabat, and Newman (13) found that incubation up to 48 hours instead of the 6 to 15 hours recommended by Gomori (7) for acid phosphatase showed some of Gomori's negative tissues to be weakly positive. Our criterion of positivity also differed from that of previous authors. Thus the photographs given by Gomori (6) show that some of the cell types that he considered negative for alkaline phosphatase had part of the nucleus, probably the nucleolus and some chromatin, definitely stained, although other parts of the nucleus and the cytoplasm were free of the precipitate. Such cells were entered in our observations as moderately positive, and only complete absence of a precipitate was considered to be negative. Moog (12) could always find a minimal nuclear stain in her negative cells. Thus we dealt with smaller concentrations of the enzyme than did some of the previous workers. In the epidermal cells, in which our chief interest lay, alkaline phosphatase, when present, was most concentrated in the nucleoli, next richest in the chromatin, and least abundant in the cytoplasm.

Our results are subject, of course, to the accuracy of the histochemical test. Fell and Danielli (5), for example, doubt the exactness of the localization of phosphatase activity by this means.

The distribution of alkaline phosphatase in the skin has been studied before. Gomori (6) reported all the skin except its contained capillaries negative for alkaline phosphatase in a number of species, including several rodents. On examining human skin, Bourne (3) found strong positive tests for the enzyme only in sebaceous glands and the central part of the hair sheath, while the basal layer of the epidermis and the connective tissue below the epidermis gave no reaction. In the embryonic chick, Moog (12) noted that the originally high alkaline phosphatase content of both the ectodermal and mesodermal portions of the skin was completely lost by the end of the first week. Approximately the same was true for acid phosphatase. Fell and Danielli (5) found the reaction for alkaline phosphomonoesterase in healing wounds and burns of the rat to be most definite at first in the polymorphonuclear leucocytes of the scab, but later intense in a collar of regenerating connective tissue below the scab. When the collagen fibers began to form a deep stain was to be found in the fibroblasts, fibers, and capillaries. At this same time a collar of epidermal cells above the collar of positive dermal cells also gave a positive test for phosphatase. Our results may well be examined in the light of this regenerative reaction to a noncarcinogenic stimulus.

There were 3 essential features in the reaction of the skin phosphatase to methylcholanthrene in benzene: (a) Considerable phosphatase activity was early assumed by the nuclei of the epidermal basal cells and by the cells of the reticular layer of the dermis; (b) as epidermal hyperplasia progressed and the hair follicles were destroyed, the alkaline phosphatase became less concentrated in the epidermis and the reticular layer, but it was still abundant in the basal cells wherever a chance capillary lay close to the epidermis; (c) in the carcinoma and papillomas induced by methylcholanthrene the reaction for the enzyme was very intense both in the stroma and in the epidermal cells lying near it.

On the border of the hyperplastic region of low alkaline phosphatase activity the reticular layer was still heavily stained, and above it the epidermal cells likewise gave evidence of considerable activity of the enzyme. The resemblance to the ring of cells of high phosphatase activity underneath a wound (5) was very close.

It is evident that alkaline phosphatase is somehow concerned in the regeneration of skin. Perhaps it takes some part in the differentiation of the newly formed cells. Moog (12) has recently pointed out that the phosphatases that are abundant in early embryonic cells of the chick are probably concerned in chemical differentiation, and that they should be considered as entities distinct from the phosphatases that appear later as products of differentiation of the various cell types. Perhaps the alkaline phosphatase that becomes more abundant in the skin near healing wounds and in early stages of the hyperplasia induced by methylcholanthrene may be regarded as closely akin to, or identical with, the phosphatase of chemical differentiation in early embryogeny, on the assumption that the young mouse has such an enzyme. The capacity for forming this same enzyme is still present in later stages of massive hyperplasia caused by methylcholanthrene, as may be seen in epidermal cells in the neighborhood of strongly positive dermal elements. The enzyme present in great concentration in favorably situated cells of the papilloma and carcinoma studied may likewise be looked on as of this type.

This probably does not hold for the alkaline phosphatase found in osteogenic tumors of the chicken and mouse by Kabat and Furth (10), for in these growths the presence of the enzyme was doubtless related to the immediately preceding state of differentiation of the cells. These authors found no conspicuous amounts of alkaline phosphatase in 3 nonosteogenic chicken sarcomas, a methylcholanthrene mouse sarcoma, or a carcinoma of the human breast, although adenomatous and normal lactating breasts contained considerable phosphatase. Longer incubation would probably have given positive results, in the light of our work. Landow, Kabat, and Newman (11) observed that alkaline phosphatase activity in the cells of tumors of the nervous system of man, cat, mouse, and chicken was usually about that of normal cells of the type from which the tumor cells were derived. Acid phosphatase had about the same distribution and activity in neoplasms of the nervous system as in the normal tissues, according to Wolf, Kabat, and Newman (13), except that the tumors were usually more strongly positive, especially in the nuclei. The variability in the change of phosphatase activity from the normal to the neoplastic condition, as measured by chemical means in a number of species and tissues, has been set forth by Greenstein (8). It has been suggested by Woodard (14) that alkaline phosphatase, histochemically demonstrable in the nuclei of rat liver cancer produced by feeding *p*-dimethylaminoazobenzene, underwent the chemically-observed tenfold increase as a compensation for a possible interference in the production of a substrate for the enzyme.

The direct relation of the proximity of epidermis and phosphatase-active dermal elements to the intensity of the alkaline phosphatase reaction in the former suggests a substance of limited diffusibility that passes *in vivo* from dermal cells of certain types and physiological states to the epidermal cells directly above. The substance may be phosphatase, a precursor of the enzyme, or an agent in its synthesis. That the hypothetical substance, or components of the stain, did not diffuse during the incubation or the staining, to be absorbed on receptive epidermal cells, is suggested by the polarity of its distribution from the dermis to the epidermis. This observation of the relation of the epidermal phosphatase to the nearness of rich stroma is similar to that made by Caspersson and Santesson (4), concerning the concentration of ribonucleic acid in cells of epithelial cancer cords. Yet the two situations are not strictly parallel, for the ribonuclease-pyronin test for ribonucleic acid in epidermis made hyperplastic with methylcholanthrene (1) does not reveal any dependence of cytoplasmic ribonucleic acid concentration on particular elements of the dermis, other than that the basal cells are usually richer in the acid than are the suprabasal cells.

In view of the facultative nature of the occurrence of the enzyme in cells of the methylcholanthrene-hyperplastic epidermis and the benign and malignant skin tumors, no positive statements can be made about the necessity of the enzyme in histochemically demonstrable quantity for the cells, or even about the production of the enzyme by the epidermal cells. There are definite limits to the sensitivity of histochemical tests such as this for alkaline phosphatase. Small amounts of the enzyme would not necessarily be detectable even on very prolonged incubation, because a given molecule of alkaline phosphatase seems to possess the capacity to hydrolyze only a limited number of substrate molecules (9).

The similarity in degree of phosphatase activity in the carcinoma and the papilloma suggests the absence of a relationship between the concentration of the enzyme and the possession of normal or abnormally multiple-stranded chromosomes by the cells. It will be recalled that the papillomas examined for chromosomal enlargement showed only about 1 per cent of metaphases with enlarged chromosomes, while the value for carcinomas was about 75 per cent (2).

SUMMARY

A histochemical study was made of alkaline phosphatase in mouse skin undergoing carcinogenesis brought about by applications of methylcholanthrene in benzene. By the second and third days after the beginning of treatment, considerable phosphatase activity was assumed by the nuclei of the epidermal basal cells and by the reticular layer of the dermis. As epidermal hyperplasia progressed and the hair follicles were destroyed, alkaline phosphatase became less concentrated in the epidermis and the reticular layer, but it was still abundant in the skin on the edge of the region of greatest histological reaction to the carcinogen, much like the collar of positive cells about a healing wound. The enzyme was abundant in the basal cells in direct proportion to the proximity of positive dermal elements, such as chance capillaries. In the carcinoma and papillomas studied the alkaline phosphatase reaction was very intense both in the stroma and in epidermal cells lying adjacent to the stroma, but the enzyme was practically absent from cells far removed.

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The Effect of Certain Lipids on the Carcinogenicity of *p*-Dimethylaminoazobenzene*

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Recently 0.06 per cent of *p*-dimethylaminoazobenzene was fed to rats in a synthetic diet containing 5 per cent of hydrogenated coconut oil as a source of fat, and the incidence of hepatic tumors found to be only 8 per cent or less by 6 months, in contrast to the usual incidence of 60 per cent at this time when the fat in the diet was corn oil (6). The effect of the hydrogenated coconut oil persisted in the presence of amounts of ethyl linolate sufficient for the growth and well-being of rats on a fat-free diet, and a series of analyses failed to reveal any significant differences in the stability of the azo dye when it was dissolved in the two oils and incorporated into diets. The failure of liver tumors to develop in the presence of the coconut oil, therefore, was provisionally ascribed to some change within the animal itself.

Since the chemical differences between the two oils are great, a further inquiry has now been made into the effect on tumor formation of the appropriate single lipoidal substances involved. Thus *a*-tocopherol was studied because this vitamin is much more abundant in corn oil than in coconut oil. A diet free of fat was fed as an analog of the diet containing hydrogenated coconut oil in the sense of its deficiency in both *a*-tocopherol and autoxidizable lipids. The fat-free diet, however, was further devoid of the characteristic ingredients of the coconut oil (saturated short-chain glycerides and unsaponifiable matter) that might conceivably have exerted a protective effect. The specific effect of the short-chain glycerides was tested in a group fed synthetic trilaurin, and the effect of hydrogenation in a group fed raw coconut oil. The relative importance of corn oil and coconut oil was tested in groups fed mixtures of the two oils. Finally, the results of these variations were correlated with those obtained when the level of azo dye in the diet was lowered to 0.03 per cent in the corn oil diet, or raised to 0.12 per cent in a diet containing hydrogenated coconut oil.

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METHODS

As in our previous experiments (6, 7, 8) young, mature, albino Sprague-Dawley rats 170 to 200 gm. in weight were fed 0.06 per cent of *p*-dimethylaminoazobenzene for a period of 120 days. One group, however (Table II, group 15), received a hydrogenated coconut oil diet containing 0.12 per cent of the azo dye and another group (Table II, group 14) on a corn oil diet was given only 0.03 per cent of the dye. The animals were kept in groups of 7 and 8 in screen-bottomed cages; food and water were given *ad libitum*. The carcinogen was incorporated into the diets by dissolving it with heat in the fat involved. In the diet that contained no added fat, an acetone solution of the dye was mixed with the diet and the solvent evaporated before a fan. The rations were mixed in amounts sufficient for 2 to 4 weeks and stored at 0° to 5° C. After 120 days the livers were examined by laparotomy (7) and the animals continued for an additional 2 months on the same diet as before, but minus the azo dye. At 6 months a final examination of the livers was made. The composition of the various diets is indicated in Table I. With the exception of diets 11 and 12, which contained 2 per cent of the rice bran concentrate "Vitab" as the source of the B vitamins, all diets were supplemented with the following levels of crystalline B vitamins per kilogram: 3.0 mgm. thiamin chloride, 2.0 mgm. riboflavin, 2.5 mgm. pyridoxine hydrochloride, 7.0 mgm. calcium pantothenate, and 30.0 mgm. choline chloride. Each rat received also 1 drop of halibut liver oil monthly.

Since hydrogenated coconut oil is very low in tocopherol (6), the effect of antioxidant on tumor formation with this fat was tested by adding 80 mgm. of synthetic *dl-a*-tocopherol to each 100 gm. of hydrogenated coconut oil. This is approximately equivalent to the amount of tocopherol found in corn oil (10). In another series the corn oil was chromatographed to remove antioxidants (11). Fifty grams of fat dissolved in 450 gm. of petroleum ether were forced through a column (2.5 × 29 cm.) containing activated Al_2O_3 and then through another column of like

dimensions containing a mixture of 12.5 gm. of J-neutrol and 25 gm. of Hy-Flo Super Cell. The fats were finally freed from solvent by gentle heating under reduced pressure. Fresh batches of fat were prepared at weekly intervals. As a control, 1 group of rats was fed hydrogenated coconut oil that had been chromatographed in a like manner. The synthetic trilaurin employed in this study was prepared by heating equivalent quantities of lauric acid and glycerol for 6 hours at a temperature of 200° C. in an atmosphere of CO_2 (3).

Table I: Composition of Diets *

Constituents	Diets, gm./kgm.													
	1 & 13	2	3	4	5	6	7	8	9	10	11	12	14	15
Cerelose †	790	790	790	790	790	790	790	790	815	840	770	770	790	790
Casein (purified ‡)	120	120	120	120	120	120	120	120	120	120			120	120
Casein (crude)											120	120		
Salts mixture	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Corn oil (Mazola)	50	50 §				40	10				50		50	
Coconut oil								50						
Hydrogenated coconut oil			50	50 §	50	10	40					50		50
Trilaurin									25					
dl-α-Tocopherol					0.04									
Rice bran concentrate ‖											20	20		
p-Dimethylaminoazobenzene	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.3	1.2

* With the exception of diets 11 and 12 each kilogram of diet was supplemented with the following amounts of crystalline B vitamins: 3.0 mgm. thiamin chloride, 2.5 mgm. pyridoxine hydrochloride, 2.0 mgm. riboflavin, 7.0 mgm. calcium pantothenate, and 30.0 mgm. choline chloride.
† Pure glucose monohydrate obtained from Corn Products Refining Company.
‡ For preparation see Reference 6.
§ Chromatographed oil (see text).
‖ "Vitab Rice Bran Concentrate," obtained from National Oil Products Co., Harrison, N. J.

Table II: The Effect of Certain Lipids on the Carcinogenicity of *p*-Dimethylaminoazobenzene

Group *	Diet	Average starting wt., gm.	Average wt. at 4 mo., gm.	Average food consumption, gm./rat/day	Survival † at 4 mo.	Hepatomas ‡ at 4 mo.	Hepatomas ‡ at 6 mo.	Cirrhosis at 4 mo.	Dermatitis §
1	Corn oil	194	200	10.1	15/15	5/15	11/15	Moderate-severe	0
2	Corn oil (chromatographed)	174	226	10.5	14/15	3/14	12/14	" "	0
3	HCNO ‖	183	219	11.3	14/15	0/14	1/14	None-slight	+
4	HCNO (chromatographed)	191	228	10.1	12/15	0/12	1/12	None	+
5	HCNO + α-Tocopherol	197	255	13.5	15/15	0/15	1/15	"	++
6	4 parts corn oil, 1 part HCNO	185	212	11.3	16/16	7/16	10/16	Moderate-severe	0
7	1 part corn oil, 4 parts HCNO	188	223	12.9	15/15	1/15	5/15	None-slight	0
8	Coconut oil	188	235	11.1	14/15	1/14	6/14	" "	+
9	Trilaurin	189	250	11.5	14/15	2/14	5/14	" "	++
10	Low fat	185	207	11.8	13/15	2/13	9/13	" "	++
11	Corn oil + "Vitab"	169	169	9.0	14/16	13/14	14/14	Moderate-severe	0
12	HCNO + "Vitab"	182	201	10.0	14/15	3/14	10/14	None-moderate	+++
13	Corn oil (0.06% azo dye)	151	188	11.1	15/15	5/15	12/15	Moderate	0
14	Corn oil (0.03% " ")	163	242	14.3	14/15	0/14	0/14	None-slight	0
15	HCNO (0.12% " ")	149	185	7.5	12/15	1/12	2/12	None-slight	+

* Groups 1 to 12 constitute one series of experiments and are directly comparable; groups 13 to 15 comprise a second series.
† Survival = number living over number at start.
‡ Hepatomas = number with hepatomas over number surviving at 4 months.
§ Dermatitis of paws and tail is indicative of a linoleic acid deficiency.
‖ HCNO = Hydrogenated coconut oil.

RESULTS

The general physical condition of the rats on most of the diets was good. The animals ate 9 to 10 gm. of food daily, they gained in weight, and the survival at 4 months ranged from 80 to 100 per cent (Table II). Deaths exceeding 1 rat per group were noted in only 3 of the 15 experimental groups, the lowest food intake and poorest survival being in the group fed 0.12 per cent instead of 0.06 per cent of the azo dye. As noted several times previously (7, 8) the rats fed the rice bran concentrate "Vitab" plus 12 per cent crude casein and 5 per cent corn oil (Table II, group 11) developed tumors more rapidly and in higher percentage than the animals fed mixtures of synthetic B vitamins in diets containing purified casein. Since the animals in group 11 did not appear well during the experiments, single doses of 10 μgm. of riboflavin were given to each rat in groups

11 and 12 after 2 and 3 months. Although the rats receiving rice bran concentrate plus the hydrogenated coconut oil (Table II, group 12) were in good condition, they were given the same amount of riboflavin as the animals in group 11 in order to maintain the same vitamin intake in comparable groups. The rats fed the diet containing the rice bran concentrate and corn oil were the only ones that failed to gain in weight during the 4 months that the dye was fed, and they consumed only 9.0 gm. of food daily in contrast to the 10 or more gm. daily consumed by the others. Thus a higher incidence of tumors had developed in this group in spite of a reduced caloric intake and a reduced consumption of carcinogen, two factors that ordinarily tend to minimize rather than to enhance carcinogenesis. The cocarcinogenic character of the ingredients of this diet therefore appeared to be even greater than the observed tumor incidence suggests. The incidence of tumors in the rats fed the control synthetic diet plus corn oil (Table II, group 1) was 33 per cent at 4 months and 73 per cent at 6 months. The incidence of tumors previously observed on this diet ranged from 53 per cent to 67 per cent at 6 months (6, 8).

The effect of hydrogenated coconut oil.—Previously when hydrogenated coconut oil was fed in the synthetic diet instead of corn oil, the rate of tumor formation due to *p*-dimethylaminoazobenzene was considerably delayed or suppressed entirely (6). In the present series the incidence of tumors in the rats fed hydrogenated coconut oil was 8 per cent or less by 6 months (Table II, groups 3, 4, and 5) in contrast to 73 to 86 per cent when corn oil was fed (Table II, groups 1, 2, and 13). The very great anticarcinogenic potency of hydrogenated coconut oil was further demonstrated in a group of rats fed the oil plus 0.12 per cent of *p*-dimethylaminoazobenzene instead of the usual 0.06 per cent. Most observers appear to agree that it is not feasible to feed concentrations of dye above 0.06 per cent, because many rats then fail to survive long enough to develop tumors (5). This observation was made with natural oils such as olive oil. However, when hydrogenated coconut oil was given (Table II, group 15), 12 of 15 rats fed 0.12 per cent of dye survived for 4 months. Only 2 of these had a tumor by 6 months, but the survival of this group after laparotomy was relatively poor. As might be expected, the concentration of azo dye determines the number of tumors that develop when the other constituents of the diets are equal. Rats fed the synthetic diet plus 0.03 per cent *p*-dimethylaminoazobenzene failed to develop tumors by 6 months as contrasted to the control group in this series, which had a tumor incidence of 80 per cent when 0.06 per cent of the dye was fed (Table II, groups 13 and 14).

When mixtures of corn oil and hydrogenated coconut oil were fed, the response tended to be characteristic of the major component of the mixture, with a small amount of corn oil exerting more effect than a small amount of hydrogenated coconut oil. Thus the ingestion of 1 per cent of corn oil and 4 per cent of coconut oil evoked a tumor incidence of 33 per cent by 6 months (Table II, group 7), in contrast to 8 per cent when 5 per cent of the hydrogenated coconut oil was ingested (Table II, group 3). On the other hand, the presence of 1 per cent of hydrogenated coconut oil in addition to 4 per cent of corn oil in the diet resulted in a tumor incidence of 63 per cent (Table II, group 6) in contrast to an incidence of 73 to 80 per cent when 5 per cent of corn oil was fed in the present series (Table II, groups 1 and 13), or to an incidence of 53 to 66 per cent in previous series (6, 8). These latter differences can hardly be regarded as significant.

The effect of the two oils was also noted in diets containing rice bran concentrate, although to a lesser degree than when synthetic B vitamins were fed. At 6 months the incidence of hepatic tumors was 100 per cent when corn oil was fed and 71 per cent when hydrogenated coconut oil was fed; at 4 months the figures were 93 per cent and 21 per cent respectively (Table II, groups 11 and 12). It appears probable that a more striking difference in the ultimate incidence of tumors could be demonstrated with this diet if the concentration of carcinogen in the diet were lowered, or if the carcinogen were fed for a shorter period of time.

The protective effect of the hydrogenated coconut oil was apparent not only in the numbers of tumors that developed, but also in other ways. The livers of rats fed corn oil and *p*-dimethylaminoazobenzene invariably showed a definite gross nodular cirrhosis, which frequently was severe. The livers of the rats fed hydrogenated coconut oil were either free from gross nodular cirrhosis or the cirrhosis was very mild. In general the rats fed coconut oil ate more food and gained more weight than those fed corn oil. Thus they actually ingested more carcinogen, for previous analyses have indicated that the azo dye is stable in both diets (6).

Constituents of coconut oil.—From a chemical point of view the anticarcinogenic effect of hydrogenated coconut oil could result from one of two causes: (a) the presence of something in the oil that suppresses carcinogenesis due to *p*-dimethylaminoazobenzene, or (b) the absence of some dietary ingredient essential for this process (6). The fatty acid that is most abundant in ester form in coconut oil is lauric acid. Accordingly pure synthetic trilaurin was incorporated in the diet at a level of 2.5 per cent. The rats fed this diet ingested roughly the same amount of lauric acid in ester form as those receiving 5 per cent of

hydrogenated coconut oil. The incidence of hepatic tumors on the trilaurin diet was 35 per cent (Table II, group 9). An incidence of 69 per cent was observed when no fat was fed (Table II, group 10). This single observation, therefore, suggests that trilaurin retards tumor development slightly. Since, however, the percentage incidence of tumors was significantly higher on trilaurin than on hydrogenated coconut oil, 35 per cent and 8 per cent respectively, it is evident that the effect of the hydrogenated coconut oil must have been due also to factors other than glycerides containing lauric acid.

The incidence of tumors was higher on raw coconut oil than on the hydrogenated product, 43 per cent *vs.* 8 per cent (Table II, groups 8 and 3). Ordinary coconut oil contains from 4 to 9 per cent of oleic and linoleic acid glycerides. However, previous experience with supplements of ethyl linolate (6) and the results on certain diets of the present series (Table II, groups 7, 9, and 10) seem to eliminate these acids as stimulating factors. Other possibilities are that the process of hydrogenation might destroy stimulating principles in the unsaponifiable fraction, or give rise to inhibitors not present in the original oil.

α-Tocopherol.—Apparently the α-tocopherol present in the corn oil does not exert any effect on the carcinogenicity of *p*-dimethylaminoazobenzene. When most of the tocopherol was removed chromatographically on Al_2O_3 the incidence of hepatic tumors was unchanged (Table II, groups 1 and 2). This procedure likewise failed to disturb the protective effect of the hydrogenated coconut oil (Table II, groups 3 and 4). The addition of 0.8 mgm. of synthetic *dl*-α-tocopherol per gram of hydrogenated coconut oil, equivalent to the usual amount found in corn oil (10), failed to increase the incidence of tumors (Table II, groups 3 and 5). As a matter of fact, the rats on hydrogenated coconut oil and α-tocopherol ate the most food (and therefore the most carcinogen), they gained the most weight, and their survival was 100 per cent. α-Tocopherol is known to be a powerful antioxidant, and its capacity to preserve carotene in the presence of unsaturated acids has been demonstrated in the digestive tract as well as *in vitro* (9). Since carotene is at least as autoxidizable as *p*-dimethylaminoazobenzene, and since both substances are similar in solubility, it would appear most unlikely that the failure of tumors to develop when α-tocopherol is fed with hydrogenated coconut oil could have been due to autoxidation in the digestive tract.

Essential fatty acids.—It was previously noted that supplements of ethyl linolate to a diet containing hydrogenated coconut oil failed to increase the incidence of hepatic tumors (6). Table II presents further evidence that the formation of hepatic tumors does not depend upon the development or prevention of the Burr and Burr syndrome characteristic of a deficiency in essential fatty acids. The amounts of these acids were very low in many of the diets of the present series, and after 2 to 3 months these adult rats developed a notable scaliness of the paws and tail that persisted throughout the experimental period. The symptoms were definite in the groups fed hydrogenated coconut oil, in which the incidence of tumors was very low; no symptoms appeared in the groups fed corn oil, in which the incidence of tumors was high. However, the characteristic scaliness was also evident in the groups fed trilaurin or a diet free from fat, on which latter diet the incidence of tumors reached 69 per cent (Table II, group 10). The scaliness was particularly severe in the rats fed hydrogenated coconut oil and the rice bran concentrate, and the incidence of hepatic tumors in this group was 71 per cent (Table II, group 12). When 1 per cent of corn oil was added to a diet containing 4 per cent of hydrogenated coconut oil the symptoms of linoleic acid deficiency were prevented completely, yet the incidence of tumors was 33 per cent, considerably less than the incidence of 69 per cent in the rats fed the diet free of fat, on which the symptoms of deficiency were severe. Within any group the degree of scaliness of the paws and tail was no worse in the rats that failed to develop hepatic tumors than in those in which neoplasms were found. Thus no particular correlation was evident between the degree of linoleic acid deficiency and carcinogenesis.

DISCUSSION

The present series of experiments does not reveal the means by which the development of hepatic tumors is retarded when hydrogenated coconut oil is fed, although several possible explanations originally suggested now appear less probable. One was that the hydrogenated coconut oil may be deficient in something needed for tumor development and present in corn oil. When 1 per cent of corn oil was fed in the presence of 4 per cent of hydrogenated coconut oil, the incidence of tumors was 33 per cent as compared to 8 per cent when only the hydrogenated coconut oil was fed. The higher tumor incidence on unhydrogenated as compared to hydrogenated coconut oil might suggest the presence of some essential in raw coconut oil also. However, the incidence of tumors was no greater on 5 per cent corn oil than on the fat-free diet, a result that tends to discount the importance of tumor-promoters in the corn oil. Incidentally, the large number of tumors developing on the fat-free diet indicates that dietary fat is not indispensable for the absorption of *p*-dimethylaminoazobenzene, and it might even suggest that fat plays no very great role in the amount of dye that is absorbed.

Preliminary experiments (6), since amply confirmed, fail to reveal any great difference in the amount of dye remaining in the digestive tract whether hydrogenated coconut oil or corn oil is fed.

The anticarcinogenic effect of hydrogenated coconut oil does not appear to be due to a specific deficiency of either α-tocopherol or of linoleic acid, nor does it appear to depend entirely upon the lauric acid esters present. Trilaurin was less anticarcinogenic than hydrogenated coconut oil. The lauric acid glycerides, however, may have contributed something to the anticarcinogenic character of the oil, for fewer tumors developed in rats fed trilaurin than in those on a fat-free diet or on one containing corn oil.

The present experiments do not suggest that the differences in carcinogenicity observed are due to differences in the stability of the azo dye in the digestive tract, as assumed by György and his associates (4) for other fats. Hydrogenated coconut oil itself is not an autoxidizable oil and certainly the mixture of hydrogenated coconut oil and α-tocopherol is even more resistant to oxidation. If the azo dye is destroyed in the upper part of the digestive tract it should nevertheless be more stable in hydrogenated coconut oil than in corn oil; it would certainly be more stable in the mixture of hydrogenated coconut oil and α-tocopherol. Therefore, if the stability of the azo dye in the digestive tract played a major role, a high incidence of tumors should have developed in rats fed the hydrogenated coconut oil rather than the low incidence actually observed.

Frazer (1, 2) has presented evidence that the partition of absorbed fat between the portal and lymphatic systems may be affected by the nature of the fat fed. Thus rats fed a hydroxy azo dye, scarlet red, dissolved in olive oil deposited dye mainly in the fat depots, especially when the action of pancreatic lipase was inhibited by feeding a detergent. When excess pancreatic lipase was fed, or oleic acid was substituted for the olive oil, the dye was deposited chiefly in the liver. It is conceivable that *p*-dimethylaminoazobenzene may suffer a similar partition and that a major portion might be carried through either the portal or lymphatic system, depending upon the type of lipid fed. Other things being equal, one would expect the incidence of hepatic tumors to depend upon the amount of carcinogen that reaches the liver. Furthermore, the opportunities for an extrahepatic destruction of the azo dye would be much greater if the dye passed through the lymphatic system into the general circulation rather than directly to the liver through the portal vein. The extrahepatic destruction of approximately half of the *p*-dimethylaminoazobenzene normally reaching the liver could produce the inhibitory effect observed with hydrogenated coconut oil, since it was observed in the present study that rats fed only 0.03 per cent of the azo dye instead of the usual 0.06 per cent in a diet containing corn oil did not develop any tumors by 6 months.

SUMMARY

Fifteen groups of 15 rats each were fed various lipids in synthetic diets containing 0.06 per cent *p*-dimethylaminoazobenzene for 4 months followed by the dye-free diets for 2 more months. The strong anticarcinogenic effect of 5 per cent of hydrogenated coconut oil was confirmed with an incidence of hepatic tumors at 6 months of 8 per cent or less. When the hydrogenated coconut oil was replaced by corn oil, the tumor incidence increased to 73 per cent. The removal of antioxidants from either oil did not affect these tumor incidences. Likewise the addition of α-tocopherol to hydrogenated coconut oil had no effect. When mixtures of the two oils were fed the response tended to be characteristic of the major component of the mixture, with a small amount of corn oil exerting more effect than a small amount of hydrogenated coconut oil.

The formation of hepatic tumors on the diets studied did not depend upon the development or prevention of the syndrome characteristic of a deficiency of essential fatty acids. Relatively slight protection against hepatoma formation was obtained with diets containing 2.5 per cent trilaurin, the equivalent of the lauric acid contained in 5 per cent hydrogenated coconut oil. Similar results were obtained with raw coconut oil. A tumor incidence of 69 per cent was obtained with a diet free of added fat, demonstrating that dietary fat is not indispensable for the action of the dye. High tumor incidences were observed with both corn oil and hydrogenated coconut oil when they were fed in diets containing crude casein and rice bran concentrate. A very low tumor incidence still occurred in rats fed a diet containing hydrogenated coconut oil and 0.12 per cent *p*-dimethylaminoazobenzene. No tumors were found in rats fed a corn oil diet with only 0.03 per cent of the azo dye. It is suggested that the partition of dye between the portal and lymphatic systems (Frazer) may be affected by the nature of the fat fed, with subsequent differences in metabolic breakdown.

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Some Factors That Influence the Growth of Neoplastic Cells*

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It has been suggested that the formation of a cancer occurs not as a continuous single process but rather as a series of biological changes (3, 6, 13, 21). The various steps involved are a matter of conjecture, but presumably neoplastic cells must first be formed and then they must proliferate to form a grossly recognizable tumor. The present communication is concerned with some of the factors that influence tumor formation, with special emphasis on the proliferation of the established neoplastic cell. The agents used included croton oil, naphthoquinone, sodium sulfide, and tissue damage as produced by mechanical wounding.

The application of certain chemical irritants (2, 3), heat (8), cold (1), or physical trauma (7, 13, 21) to a region previously treated with a subcarcinogenic amount of hydrocarbon is known to precipitate the formation of tumors in a relatively short period of time, but there is some question whether the secondary treatment completes the processes involved in the actual formation of the cancer cell or whether it is in some manner responsible for the proliferation of cancer cells already formed. Hence the effect of mechanical wounding was also determined on the growth of neoplastic cells whose existence was well established.

The effect of chemical and physical agents on carcinogenesis of the skin by methylcholanthrene.—Two series of 100 young adult albino mice were kept on wood shavings in metal box cages and were given dog biscuit and water *ad libitum* throughout the experiment. The mice were painted twice weekly with a solution of methylcholanthrene applied with a camel's hair brush to the interscapular area. The length of the initial treatment with the hydrocarbon varied in the two series according to the strength of the solution and the susceptibility of the mice. They were then divided into groups of 25 each. In each of the series one group was set aside as a control and received no further treatment, while in the remaining groups the area of skin that had previously been painted with the hydrocarbon was subjected to various further treatments. The animals were carefully examined every 2 weeks for the appearance of tumors. The details of dosage and time relationships are presented in Table I.

Croton oil and its resin were tested because of their pronounced augmenting effect on carcinogenesis as previously described (2, 3). A solution of naphthoquinone was used because it is an irritant known to inactivate certain enzymes (20). Sodium sulfide was applied because it represents a different type of chemical irritant, and incisions repeated at regular intervals were employed because tumors have been reported to occur in scars and healing wounds (7, 21, 22, 24). In the latter group 3 or 4 parallel skin incisions about 2 cm. in length, which penetrated the dermis, were made with a sharp scalpel.

The effect of these various forms of irritation on areas previously treated with methylcholanthrene is shown in Table I. No visible tumors were present in any of the animals when the applications of hydrocarbon were discontinued at the end of the preliminary treatment, and only a few neoplasms eventually developed in the controls. However, when a 0.1 per cent solution of naphthoquinone was applied subsequent to the hydrocarbon treatment many tumors developed. Thus 14 carcinomas and 4 papillomas arose in this group (group 8) as compared to 5 epitheliomas and 7 papillomas observed in the control group. This finding is of interest not only because it is new but also because the effect is comparable to that obtained with croton oil, a known active epicarcinogen (3). In series I, the application of croton oil resin stimulated tumor production to the extent that there were 4 epitheliomas and 14 papillomas as compared to only 1 epithelioma in the control group 4 months after discontinuing the hydrocarbon treatment; in series II, after 6 months there were 14 epitheliomas and 8 papillomas in the group that received croton oil in contrast to 5 cancers and 7 papillomas found in the control group. In fact croton oil was almost as effective in developing the tumors as the continued application of the methylcholanthrene itself (group 6). This parallels the experience of Berenblum (2, 3). Chronic physical trauma in the form of repeated incisions of the skin had a slight but definite augmenting effect on tumor formation. This effect appeared early, and in the first 2

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months following the discontinuation of hydrocarbon treatment it seemed to be as effective as the croton resin applications. However, in spite of continued treatment, a regression of tumors was observed; there were 8 papillomas after 2 months and only 6 after 4 months. All tumors were localized in or very close to the area of the scar. Any experiment in which repeated incisions are attempted is apt to be complicated by infection of the area, and this could have an adverse effect on tumor formation. Furthermore, multiple incisions are apt to result in the physical destruction or elimination of small tumors. Our results, although limited, suggest that wound healing has at least a transient augmenting effect on the development of tumors, and confirm the observations of other investigators (7, 13, 21, 22).

TABLE I: THE EFFECT OF CHEMICAL AND PHYSICAL AGENTS ON CARCINOGENESIS OF THE SKIN BY METHYLCHOLANTHRENE

(The croton oil resin was dissolved in ethyl alcohol; the naphthoquinone and croton oil were applied as solutions in benzyl alcohol)

Strain of mice	Initial treatment	Group	Subsequent treatment	Incidence of tumors *											
				1 mo.			2 mos.			3 mos.			4 or 6 mos. †		
				Ca	P	N	Ca	P	N	Ca	P	N	Ca	P	N
ABC Stock (Series I)	0.3% methylcholanthrene in benzene applied twice weekly for 8 weeks	1	None	0	0	25	0	0	25	1	0	24	1	0	24
		2	Sat. sol. of Na_2S once weekly for 7 weeks	0	0	24	0	0	24	0	0	24	0	2	22
		3	Incisions of skin twice a month for 4 months	0	3	19	1	8	13	1	6	15	1	6	15
		4	0.1% croton oil resin twice weekly for 4 months	0	2	23	2	8	15	3	11	11	4	14	7
Strain C (Series II)	0.2% methylcholanthrene in benzyl alcohol applied twice weekly for 16 weeks	5	None	0	1	23	0	3	21	1	4	19	5	7	12
		6	Continuation with methylcholanthrene for 6 months	0	1	24	1	12	12	4	10	11	22	0	3
		7	1% croton oil twice weekly for 6 months	0	5	20	4	6	15	4	9	12	14	8	3
		8	0.1% naphthoquinone twice weekly for 6 months	0	6	19	4	4	17	4	5	16	14	4	7

* Number of months after discontinuing the initial treatment.
† The results listed for series I are for 4 months and those in series II for 6 months.
Ca = Carcinoma.
P = Papilloma.
N = Negative.

The results of the experiment with sodium sulfide also demonstrates that it is possible to have irritation without obtaining a cocarcinogenic effect. Weekly applications of sodium sulfide to the skin in amounts sufficient to produce considerable erythema did not augment tumor formation, although we do not know whether the irritation produced by this chemical was as intense, prolonged, or penetrating as that obtained by the methods that proved to be effective.

The effect of tissue damage as produced by wounding on the growth of established tumors.—Forty rats having palpable liver tumors induced by feeding *p*-dimethylaminoazobenzene were selected, and midline abdominal incisions extending to the sternum were made under ether anesthesia in such a manner that the livers could be easily inspected (17). The presence of large hepatomas having been confirmed, the wounds were closed with silk sutures. Six of the rats were given no further treatment following the first incision, and were killed after 40 days. In the remaining 34 rats, periodic irritation of the wounded area was repeated from 1 to 5 times. This treatment consisted of cutting, perforating, and drawing a threaded needle through the healing wound in numerous places at weekly intervals. The animals subjected to repeated irritation were killed at various times during the 5 week period, close inspection was made of the inner surface of the wounds, and pieces of tissue were removed for histological examination from representative sites of the wounded area.

Of the 34 rats receiving periodic irritation in the form of wounding, 6 died soon after the operation because of large liver tumors, leaving 28 for subsequent examination. In 19 of these rats, from 1 to 5 small tumor nodules were found growing in the wounds. These nodules were located in the incision itself or closely adjacent to it, and varied in size from those just visible to others that were about 3 mm. in diameter (Fig. 1). The wounds were usually bound down to the liver tumors with fresh fibrinous adhesions, and

nodules were also seen in these adhesions but no metastases were observed to any other part of the abdominal cavity. It is probable, therefore, that the tumor nodules developed from cells that reached the wound by direct contact. Histological examination demonstrated that the nodules were hepatomas identical with the primary liver tumor with which they were in contact (Fig. 2). Microscopic study of the wounds also revealed the presence of many nests of similar tumor cells of varying sizes. In fact, some wounds were literally sprinkled with nests of hepatoma cells. These tumors grew most vigorously in the fresh wounds and attained their largest size about 2 to 3 weeks after the injury. After this period the nuclei of the tumor cells became pyknotic

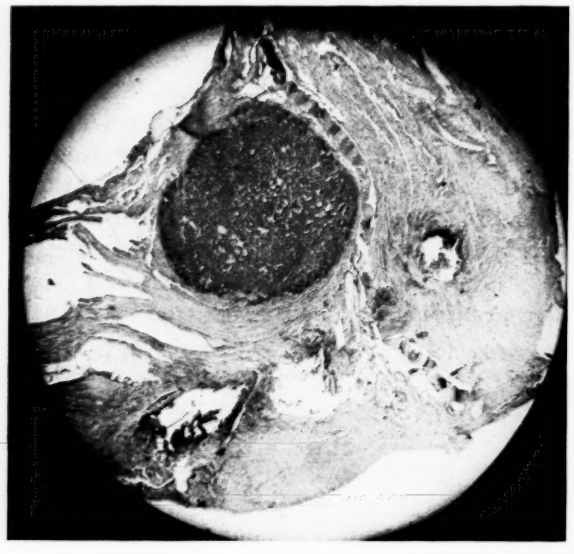

FIG. 1

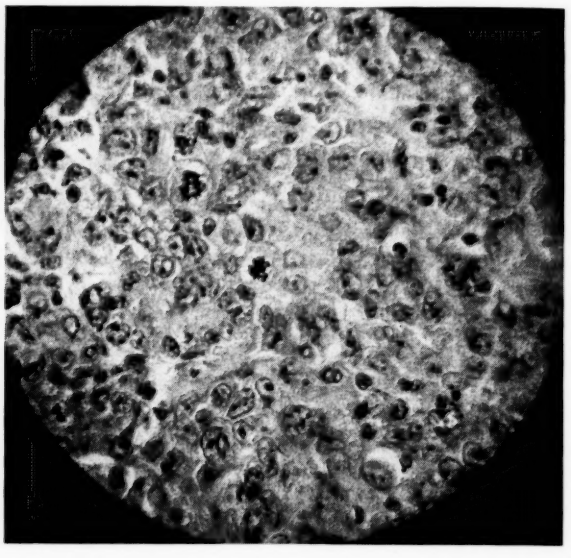

FIG. 2

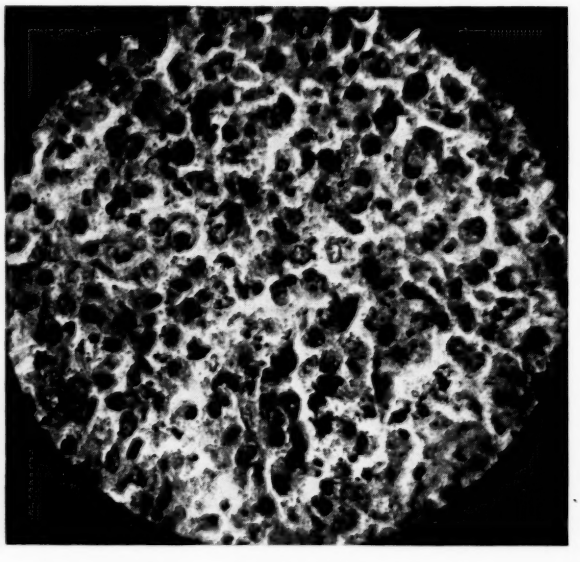

FIG. 3

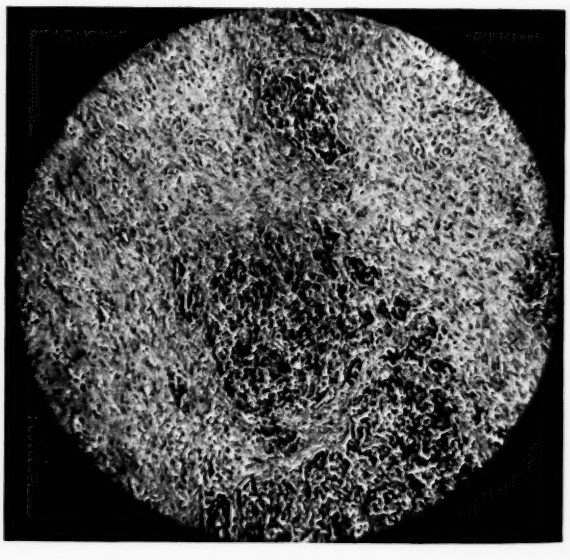

FIG. 4

FIG. 1.—Low power of hepatoma in wounded area of anterior abdominal wall of a rat. Note scar tissue from recent laparotomy incision just to right of tumor nodule. Two suture holes containing pieces of silk are also visible in picture.

FIG. 2.—High power of hepatoma removed from recently wounded area similar to that shown in Fig. 1.

FIG. 3.—This high power photomicrograph illustrates degeneration and necrosis that occurs in hepatomas after healing processes have been completed.

FIG. 4.—This shows pronounced degeneration of hepatoma found in region of an old healed abdominal incision. Note dense connective tissue that has encompassed the tumor. This is an older wound than that from which the hepatoma shown in Fig. 3 was obtained.

(Fig. 3), and regression in the older wounds was rapid (Fig. 4). No tumors were found after 40 days in the wounds of the 6 control rats whose midline incisions were not subjected to postoperative interference, and with one exception hepatomas were absent in the fully healed wounds that had been subjected to repeated injury. In one animal the hepatoma continued growing until death. The conclusion should not be drawn that all experimental tumors will regress in healed wounds. Generally the rat hepatoma does not metastasize widely, nor is it extremely invasive. It is very likely that a more malignant tumor would not be so apt to regress in a healed wound once it had attained the size achieved by some of the hepatomas observed in this experiment.

DISCUSSION

The present experiments are in harmony with the general idea that cancer formation occurs following a sequence of biological changes (3, 6, 13). These changes might be classified as follows:

I. Induction period. This is the period during which neoplastic cells are formed.

II. Critical or reversible period. This starts at the moment the neoplastic cells are formed, and represents that stage in which cellular proliferation is delicately balanced. Presumably during this phase the cells may proliferate for a time, some may die, and others may lie quiescent for varying periods. This is the transitional period, during which the cells are most susceptible to the influence of their environment. It could vary in time from a few moments to periods of weeks, months, or even years. Whether a tumor cell dies or proliferates depends upon the balance between the proliferative capacity of the cell and the local tissue resistance.

III. Period of progression. This may be considered as that period when the neoplastic cells have gained ascendancy over the forces that hold them in control. There is no sharp line between the second and third periods, but in general the latter is one of relatively unrestricted, invasive growth, during which regressions are infrequent. The exact size that a neoplasm must attain before it reaches this stage varies, no doubt, with different tumors. Indeed the separation of tumor formation into various periods is only an arbitrary scheme, intended to assist in the clarification of our views on carcinogenesis. Actually the different stages are probably not clearly separable, and within a neoplastic focus, at any period, tumor cells are being formed, others are dividing, and still others are dying. The final outcome is the result of a balance of the various factors involved.

The postulation of a second, or critical, period in the development of a tumor is supported by several types of experimental evidence. First, when methylcholanthrene is applied to the skin of mice for a time short of that necessary to induce tumors, the subsequent resumption of the hydrocarbon treatment will precipitate tumor formation even though 3 to 4 months intervene between the 2 periods of hydrocarbon application (10). Such observations suggest that the initial application of hydrocarbon produced alterations in the tissues that persisted for at least 4 months, although there is no proof that any neoplastic cells had been completely formed as the result of the initial treatment with hydrocarbon.

Rous and his associates (13, 22) have shown that wounding rabbit ears caused the appearance of papillomas at sites from which they had previously regressed. The wounding process was therefore thought to stimulate the growth of quiescent neoplastic cells. The growth of hepatoma cells in wounds in the present experiment likewise suggests the stimulating influence of irritation on the proliferation of established neoplastic cells.

It seems likely that the noncarcinogenic agents that favor the growth of neoplastic cells during the critical period exert their effects on *established* cancer cells rather than on the actual formation of such cells, since croton oil applied to the skin of mice prior to benzpyrene had no effect on tumor formation (3). Furthermore, if heat, cold, or trauma was applied during the induction period the process of carcinogenesis was actually retarded, presumably by an interference with some of the biochemical changes necessary in the development of the neoplastic cell (23).

In an investigation in which the growth rates of experimental tumors were closely followed, Blum (4) demonstrated that the growth rate of the neoplasm did not remain constant throughout the development nor did it follow the same pattern in all tumors of the same type. His data suggest that opposing growth and regressive processes determine the time at which a tumor becomes established, and indicate that tumor cells do not escape and assume their own essential proliferation rates, but that the rates of growth are to a great extent dominated by the controlling influence of the tissue.

The experiments of Fischer also suggest that quiescent neoplastic cells may be stimulated to activity if certain favorable conditions are imposed (9). He transplanted pieces of apparently normal mammary tissue to other parts of the same mouse. After a few days these pieces were removed and reinoculated into other areas of the same animal and the procedure was repeated many times. Several tumors eventually grew in the region of the transplant. These results might be explained on the basis that the frequent wounding incident to the inoculations had exerted a favorable in-

fluence on the growth of resting or latent neoplastic cells present in the original transplants. The opposite effect, a regression of tumor growth in an unfavorable environment, was recently demonstrated by Briggs and Grant (5). They observed that a tumor grew well in the tail of a tadpole for several weeks but that it stopped growing even before the metamorphic regression of the tail commenced. There appeared to be some relationship between metamorphosis and the proliferation of neoplastic cells.

It is a well known fact that injury to tissues is followed by an improved blood supply, an elevated temperature, and an increase of nutritive substances to the region. Conditions favorable for cellular proliferation probably persist until the injury has been repaired. Loofbourow has described growth-promoting nucleotides produced by injured cells (11, 12), while Menkin has demonstrated stimulating agents in inflammatory exudates (14). The latter investigator injected an exudate from inflamed pleura into the ear of a rabbit and observed striking proliferation, characterized by hyperplasia and metaplasia of the normal epithelial layer and by foci of keratinization. Small nodules in the cartilage were also observed. Among other things, the exudate contained lactic acid and glucose (15, 16).

These findings support the suggestion by Potter that injury and irritation result in the breakdown of adenosinetriphosphate (18, 19). The adenosine and inorganic phosphate resulting from this primary reaction could lead to an increased glycolysis and a localized vasodilatation (18), and thus would favor the proliferation of fibroblasts as well as any neoplastic cells that might be present in the involved area. As the healing process nears completion the breakdown of adenosinetriphosphate would diminish until, finally, tissue oxidations would be able to esterify phosphate and adenosine at concentrations that are below the growth threshold. On this basis the continuation of any factor, be it gross irritation or some more subtle agent, that would accelerate the breakdown of adenosinetriphosphate or hamper its resynthesis would lead to a milieu favorable for proliferation. The subsequent growth of neoplastic cells in a healed tissue would then depend upon the inherent malignancy of the cells and the size the tumor had attained before the healing process was completed. A short period of irritation with the subsequent increase in connective tissue and decrease in blood supply would restrain the continued proliferation of the cells, whereas a longer period of healing would aid the tumor to attain a size that would be less dependent upon the local tissue environment.

There has been much uncertainty as to the connection between irritation or injury and cancer formation. Apparently irritation *per se* is not carcinogenic (23), and yet the development of tumors in old burns or other wounds is more frequent than could be accounted for by the mere laws of chance (24). These observations could be explained on the basis of the suggestions just offered.

SUMMARY

Methylcholanthrene was applied to the skin of mice for a period just short of the formation of visible tumors. The skin was then treated with naphthoquinone, croton oil, croton oil resin, or sodium sulfide, or it was subjected to frequent incisions. Many tumors developed following exposure to naphthoquinone, croton oil, croton oil resin, or to the processes of wound repair. The sodium sulfide was ineffective.

Frequent incisions made through the abdominal wall of rats with primary hepatomas resulted in nests of proliferating hepatoma cells in the regions of the wound. These neoplasms regressed during the later stages of the healing process. It is suggested that such transplanted cancer cells found a favorable environment for growth in the region of the healing wounds, and that the defense mechanism of tissues that inhibit such growth normally is decreased in areas where reparative processes are active.

These results are correlated with the suggestion that tumor formation may be divided into three phases: (a) period of induction, during which the neoplastic cell is formed; (b) critical or reversible period, in which the growth of the neoplastic cell is in delicate balance and depends upon the local tissue environment; and (c) the final period of progression, during which growth is relatively unchecked.

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Prothrombin Activity in Rats with Hepatic and Other Tumors*

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It is generally believed that the synthesis of prothrombin occurs in the liver. This has been demonstrated in several ways. The prothrombin activity of plasma is low in experimental animals after partial (17) or total (19) hepatectomy. Furthermore, when the hepatotoxins chloroform and carbon tetrachloride are administered to dogs and rats, hypoprothrombinemia results (3, 14, 18). Clinical investigators have indicated that a prothrombin deficiency arises in intrahepatic diseases such as obstructive jaundice, Laennec's cirrhosis, and acute yellow atrophy (1-3, 20). The question therefore arises, whether hepatic tumors can alter the animal's capacity to synthesize prothrombin. It is conceivable that the tumor itself might elaborate prothrombin and thereby tend to induce a state of hyperprothrombinemia. On the other hand, the presence of the tumor might interfere with the synthesis of prothrombin by the remaining normal tissue of the liver. These possibilities were tested in rats with large primary hepatic tumors induced by the ingestion of *p*-dimethylaminoazobenzene. Determinations of the prothrombin activity of the plasma from such animals were made both before and after the administration of 3,3′-methylenebis(4-hydroxycoumarin), an anticoagulant that specifically lowers the prothrombin activity of the blood (4, 15).[1] Prothrombin determinations were also made on the blood from normal rats and from rats bearing tumors in other parts of the body, before and after feeding the anticoagulant.

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[1] When this anticoagulant is given in therapeutic doses, it does not affect the red blood cells, white cells, blood platelets, blood sugar, blood nonprotein nitrogen, serum calcium, bilirubin concentrations, or the hematocrit readings (Bollmann, J. L. and Preston, F. W. The Effects of Experimental Administration of Dicumarol. J. A. M. A., **120**:1021. 1942.)

METHODS

The method of administering 3,3′methylenebis(4-hydroxycoumarin) and of determining the prothrombin time of the plasma was essentially that used in our previous studies (12). The rats were fed a semi-synthetic diet (casein 18, yeast 8, salts 4, cod liver oil 2, and dextrin 68) for at least a week prior to the initial determination of the prothrombin activity. They were then starved for 12 hours and fed 2.5 mgm. of 3,3′-methylenebis(4-hydroxycoumarin) contained in 2 gm. of food. This was consumed within 30 minutes, and 4 hours later the rats were allowed access to larger amounts of the basal ration. Twenty-four hours after the anticoagulant was consumed, blood samples were taken by heart puncture under light ether anesthesia. The clotting time of the 12.5 per cent plasma was then determined by our standard procedure (4). Determinations of prothrombin activity were made on whole plasma also, but the presentation of the data is restricted to 12.5 per cent of plasma for reasons previously stated (4, 12).

Types of tumors.—A hypoprothrombinemia was induced in rats with the following types of tumors: spontaneous mammary adenofibromas, primary skin tumors on the head due to methylcholanthrene, primary hepatic tumors due to *p*-dimethylaminoazobenzene, and transplanted Flexner-Jobling tumors. The spontaneous adenofibromas were round and discrete, and varied in diameter from 2 to 5 cm. Characteristically they were encapsulated and contained much connective tissue.

The tumors due to methylcholanthrene varied in diameter from 1.5 to 5 cm. They were rough, irregular, and papillomatous, and spread along the surface of the head and neck. The large tumors showed definite evidence of penetration into the subcutaneous tissues. These tumors had been induced by the application of a benzene solution of methylcholanthrene thrice weekly for 10 months (7), with subsequent periods of 1 to 4 months to allow the tumors to grow to a large size.

The hepatic tumors were induced by the feeding of synthetic diets containing 0.06 per cent of *p*-dimethylaminoazobenzene. The diets varied in the source of the vitamin B complex and in the nature of the fat of diet (8, 10), but all were low in vitamin K. The

azo dye was fed for 4 months, when the livers were examined for tumors by laparotomy (9). The rats were then fed the same diet as before, but not the azo dye. The individual rats selected for studies of prothrombin level all had hepatic tumors at least 1.5 cm. in diameter. Most of them had multiple tumors, some of which were several centimeters in diameter. The types of hepatic tumors encountered have been adequately described by others (5, 6, 11, 16). In some of the rats the major part of the liver appeared quite normal except for a fair-sized tumor attached to a single lobe. The opposite type of liver was that involved throughout by tumors, with little or no grossly normal liver tissue remaining. Many livers represented gradations between these two extremes.

The Flexner-Jobling tumors were inoculated subcutaneously into rats 125 to 150 gm. in weight, and at least 3 weeks elapsed between the inoculation and the first period of induced hypoprothrombinemia. The tumors varied in diameter from 2 to 5 cm. The skin above the smaller growths remained unbroken, while many of the larger ones were extensively ulcerated.

TABLE I: PROTHROMBIN TIME OF 12.5 PER CENT PLASMA FROM NORMAL AND TUMOR-BEARING RATS

	Prothrombin time (in seconds)		No. of rats	Animals above normal per cent *
	Average	Range		
Normal rats	39	34-46	360	2.5
Hepatic tumors	42	35-50	49	26.6
Epithelial tumors	39	34-42	7	0
Flexner-Jobling tumors	36	32-42	16	0

* This upper limit of "normal" plasma was arbitrarily considered to be 44 seconds.

EXPERIMENTAL

Prothrombin activity of plasma from normal and tumor-bearing rats.—The prothrombin time of 12.5 per cent plasma from normal rats ranged from 34 to 46 seconds, average 39 seconds (Table I). Only 9 of 360 samples required more than 44 seconds to clot. When large amounts of vitamin K [2] were administered, the prothrombin times of the plasmas were generally lower. The range of 15 samples was 34 to 40 seconds, average 35. In terms of prothrombin concentration, this decrease in average clotting time probably represents an appreciable change, since prothrombin concentration varies hyperbolically with clotting time, and in this particular time range a large change in prothrombin concentration produces a relatively small change in the clotting time (4).

The plasma from rats with hepatic tumors showed roughly the same range in prothrombin time as plasma from normal rats. However, 13 of 49 samples showed a clotting time above 44 seconds (Table I). The average clotting time was also somewhat longer for the cancerous plasma than for normal plasma, 42 seconds as compared to 39 seconds. The administration of 25 mgm. of 2-methyl-1,4-naphthoquinone to rats with a high prothrombin time (average 47 seconds) failed to correct the hypoprothrombinemia. Apparently the capacity to synthesize prothrombin may be impaired in animals in which a large part of the liver has been replaced by tumor. On the other hand the mere presence of a neoplasm somewhere in the body failed to affect the prothrombin levels; normal prothrombin times were observed in the plasma of rats with large growths due either to methylcholanthrene or to the inoculation of Flexner-Jobling tumor (Table I). Within the group bearing the Flexner-Jobling tumors it appeared that the prothrombin time decreased as the degree of ulceration of the tumor became more severe.

Induced hypoprothrombinemia.—Twenty-four hours after the administration of 2.5 mgm. of the anticoagulant a definite hypoprothrombinemia was observed in all rats, whether tumors were present or not (Table II). The hypoprothrombinemia induced by the anticoagulant was more pronounced in rats with hepatic tumors (163 seconds) than in normal rats of similar weight (116 seconds). Only 26 of the 463 samples from normal rats showed a prothrombin time greater than 150 seconds (6 per cent). In contrast, 12 of 24 plasma samples from the tumorous rats (50 per cent) had prothrombin times greater than 150 seconds (Table II). There is a wide variation in the degree of hypoprothrombinemia that the standard dose of the anticoagulant induces in individual rats. But in rats with tumorous livers both the extent and duration of the hypoprothrombinemia were greater than in normal rats. When 2.5 mgm. of the anticoagulant are given to a normal rat the restoration of normal prothrombin values usually occurs within 48 hours (12), but in the rats with hepatic tumors a prolonged prothrombin time frequently persisted from 60 to 72 hours after the anticoagulant had been given.

TABLE II: INDUCED HYPOPROTHROMBINEMIA IN NORMAL AND TUMOR-BEARING ANIMALS

Prothrombin time of 12.5 per cent plasma 24 hours after the administration of 2.5 mgm. 3,3′-methylenebis (4-hydroxycoumarin)

	Prothrombin time (in seconds)		No. of rats	Animals above normal, per cent *
	Average	Range		
Normal rats	116	78-215	463	6.7
Hepatic tumors	163	78-313	24	50.0
Epithelial tumors	115	96-195	15	20.0
Flexner-Jobling tumors	106	89-140	5	0

* The upper limit for "normal animals" receiving this dosage of anticoagulant was arbitrarily considered to be 150 seconds or more.

[2] The vitamin K (Menadione-Abbott) was kindly supplied by Dr. Carl Nielsen, Abbott Laboratories, North Chicago, Illinois.

Again, this tendency toward a more acute hypoprothrombinemia was not associated with all types of tumors. Rats bearing large primary epithelial tumors due to methylcholanthrene responded to the anticoagulant as normal rats (Table II), nor was there any evidence of a heightened susceptibility to the anticoagulant in rats bearing spontaneous mammary tumors or inoculated Flexner-Jobling tumors.

It was previously shown (12) that a single dose of 25 mgm. of 2-methyl-1,4-naphthoquinone would completely protect normal rats from the hypoprothrombinemia induced by 2.5 mgm. of the anticoagulant. However, the same dose of the naphthoquinone gave only slight protection to rats with hepatic tumors. The clotting time of 4 of these animals 24 hours after the ingestion of both the anticoagulant and naphthoquinone was 108 seconds compared to 40 seconds in normal animals (12). On the other hand preliminary experiments indicated that in rats bearing Flexner-Jobling or epithelial tumors vitamin K counteracts the anticoagulant as effectively as in normal animals. The increased sensitivity observed in rats with liver tumors was therefore attributed to changes within the liver itself rather than to the presence of tumor tissue *per se*.

DISCUSSION

The observations described are all in harmony with the assumption that an adequate amount of functional liver tissue is necessary for the maintenance of normal levels of plasma prothrombin. The findings indicate that hepatic tumor tissue itself does not synthesize prothrombin. In fact the reverse situation exists. Large hepatic tumors tend to replace the normal functional tissue of the liver, and a hypoprothrombinemic state results that cannot be corrected by administering high levels of vitamin K. When the anticoagulant 3,3′-methylenebis(4-hydroxycoumarin) is given to rats bearing hepatic tumors, the hypoprothrombinic response is not only of greater intensity but it persists longer.

It is not necessary to postulate any impairment in the capacity to synthesize prothrombin by those nontumor cells that still are present in the tumor-bearing liver, although such an impairment is a distinct possibility. The results observed can be attributed to a reduction in the number of normally functioning liver cells. An inadequacy in the amount of normal liver tissue would result in plasma that is borderline with respect to prothrombin activity or that is mildly hypoprothrombinemic. When the anticoagulant is given, impairment of normal prothrombin synthesis by the nontumorous liver cells is brought on, and there results the severe hypoprothrombinemia described. These observations have their counterpart in clinical reports indicating that liver cirrhosis in man produces a state of hypoprothrombinemia (1, 2, 20), which is readily augmented by administering the anticoagulant (13) and which is not corrected by vitamin K.

SUMMARY

1. The presence in the rat of spontaneous mammary tumors, of induced skin tumors, or of inoculated Flexner-Jobling tumors does not cause a prolongation of the normal prothrombin time (12.5 per cent plasma). On the other hand the presence of primary hepatic tumors due to *p*-dimethylaminoazobenzene may cause a mild hypoprothrombinemia.

2. A standard dose (2.5 mgm.) of 3,3′-methylenebis (4-hydroxycoumarin) usually causes a more severe hypoprothrombinemia in rats with primary hepatic tumors than in normal rats, or in those bearing tumors in other parts of the body. The extent and duration of the hypoprothrombinemia is probably influenced by the amount of normal hepatic tissue present.

3. While vitamin K protects normal rats against the hypoprothrombinemic action of a single dose of 3,3′-methylenebis(4-hydroxycoumarin), in rats with hepatic tumors this protective action is either lessened or abolished.

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The Urinary Excretion of Estrogens, 17-Ketosteroids, Creatine, and Creatinine in High and Low Mammary Tumor Strains of Mice*

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Since the development of strains of mice with variations in the incidence of spontaneous mammary tumors, attempts have been made to demonstrate anatomic or physiologic differences between them that might be etiologically related to tumor formation. We have searched for such a variation in the urinary excretion rates of the so-called sex hormones because of the many observations linking these agents with mammary tumor formation in susceptible strains of mice. In the present communication, comparative studies on the rates of excretion of 17-ketosteroids, estrogens, creatine, and creatinine in the urine of high (C3H) and low (C57) mammary tumor strains of mice are reported. Urinary creatinine determinations were done in order to check the accuracy of the urine collections and, since creatine excretion is influenced to some extent by the sex hormones (35), urinary creatinine-creatine ratios were obtained.

Other attempts to detect metabolic variations between high and low mammary tumor strain animals are briefly reviewed.

Anatomical observations on high, intermediate, and low mammary tumor strains of mice have been almost completely limited to the mammary glands and the endocrine system. In strains developing mammary tumors, the mammary glands develop and involute in a patchy fashion during the estrous cycle, pregnancy, and after lactation. Persistent hyperplastic areas may go on to tumor formation (13, 20, 25). Injected estrogens cause considerable proliferation in the mammary gland of a high mammary tumor strain male or female mouse, but only a minimal and variable response in the low tumor strains (22). The ovaries of the high tumor strains may show more corpora lutea as compared to the low tumor strains (26, 38). The X-zone of the adrenal cortex of a low tumor strain persists up to 100 days of age as compared to 200 days in a high tumor strain (12). A peculiar "brown degeneration" of the adrenal gland is said to occur chiefly in the high tumor strains (11), but this is not generally agreed (9). Ovariectomy in a high tumor strain female mouse at birth induces extensive adrenal hyperplasia and adrenocortical adenomas with evidence of estrogenic function at the age of about 8 months (14, 44), but this may also occur in low tumor strains (19).

Physiologic differences in hormonal sensitivity of high and low tumor strains have also been studied. Shimkin and Andervont (30) found that castrated C3H (high mammary tumor strain) mice required almost twice as much estrone as the C57 (low tumor strain) mice to produce vaginal estrus. They conclude, however, "that no correlation has been found between the manifestations of estrogenic stimulation, such as the duration of vaginal keratinization, number of estrous cycles and normality of the cycles, and the susceptibility of various strains of mice to mammary carcinoma."

Visscher and his group (42) demonstrated that high tumor strain mice (C3H) on a restricted caloric intake sufficient to prevent weight gain, did not develop any mammary tumors. Furthermore, low mammary tumor strain A mice given the same amount of food as the C3H mice gained weight. Tannenbaum (37) could prevent tumor formation in C3H mice by reducing the caloric intake at any age before the actual appearance of the tumor. It appears that some high mammary tumor strains require more food than the low tumor strains, and this increased caloric intake may possibly be related to tumor formation. In high tumor strain mice (C3H), even in the absence of mammary tumors, the red blood count and hemoglobin fall progressively with age (34). The xanthin oxidase (dehydrogenase content of the liver) is considerably lower (15) and susceptibility to the toxic effect of heptaldehyde is greater in the high tumor strains (33). The esterase

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activity of tumor susceptible mice (C3H and A) is significantly elevated in the serum and decreased in the feces as compared with a nonsusceptible strain (C57), whereas no difference appeared in the liver, kidney, and urinary esterase activity (10). The amount of fluorescent porphyrin in the lacrimal glands of mice was found to vary directly with their mammary susceptibility (16). No differences between strains have been found in the excretion of urinary protein (43), or in the ability of the livers to inactivate estrogens *in vitro* (40).

The discovery by Bittner (6-8) that the incidence of mammary tumors in the offspring of mice may be altered by the presence or absence of a factor in the mother's milk, and the subsequent studies of Andervont (1, 2) and Twombly (39) have led to a further search for metabolic differences between animals of the same strain when the rate of tumor development is altered by regulating the milk factor. Thus far two strain differences have been tested after foster nursing. Shimkin and Andervont (30) have shown that mice foster nursed by strains of opposing cancer susceptibility continue to show their strain differences in sensitivity to estrogens. The alveolar hyperplasia preceding mammary tumor formation was found by Van Gulik and Korteweg (41) to occur in the mammary glands of a low tumor strain litter foster nursed by a high tumor strain mother, and this hyperplasia was not present in the reverse situation.

MATERIALS AND METHODS

Twenty-four virgin C3H and C57 mice, 4 months old, were placed in metabolism cages that permitted the separation of urine and feces, in October, 1940, and 24 C3H mice, 6 months old and once-pregnant, were started in January, 1941. These groups were in the cages almost continuously until May, 1941, so that observations extended through a period of from 4 to 10 months. The metabolism cage, a modification of Gross and Connell's apparatus (21), consisted of a metal cage $7\frac{1}{2} \times 6 \times 6$ inches, with a bottom composed of pyrex glass rods about $\frac{1}{2}$ inch apart. The cage ordinarily housed 8 mice. A water bottle was fastened to the outside, and food was daily attached inside the cage in small bottles just large enough to admit the head of a mouse. The cage was placed over a glass funnel that connected to a side-arm device so that urine running down the side of the funnel would collect at its tip and run into the side-arm by means of capillary attraction, whereas the feces would fall straight down into a bottle at the bottom of the collecting tube. Urines were collected and measured daily, the apparatus was rinsed with water, and the urine and washings were pooled and stored in a refrigerator. Chemical determinations were made biweekly on each group and calculations were based on the number of mouse days per specimen (that is, 14 day collection period $\times$ 24 mice in the group $=$ 336 mouse days per specimen). Although this method of collection is very efficient for rats, several difficulties arise in mice that prevent a complete separation of urine and feces or a complete urine recovery. Mouse feces are fairly moist and will occasionally stick to the side of the funnel. A single mouse voiding is about 0.2 to 0.5 cc., and in running down the side of the funnel some of the urine may run into fecal matter that will absorb part of it and contaminate the rest. Small voidings may partially evaporate before they reach the collecting bottle. The presence of the proper number of mice in the cage (8 to 12) produces a greater urinary volume and therefore a more complete collection. The urine collected was clear, and rarely showed any gross fecal matter. It was estimated from creatinine determinations that about 5 per cent of the urine was recovered in apparatus washings, and total urine losses up to 30 per cent occurred. It seemed technically impossible to avoid these difficulties, so the hormonal data are also calculated per 10 mgm. creatinine in the urine. The errors in collection appear fairly constant between groups, and for comparative purposes these pitfalls do not detract from the essential observations. Incidentally, it may be noted that by offering a solution of 1 per cent NaCl and 5 per cent glucose as drinking water, urine volume could be increased up to 5 times. This technic was not used, however, since the possibility of glucose appearing in the urine would interfere with creatinine determinations.

Bills' diet (5), composed of yellow corn, 57 per cent; dried whole milk, 25 per cent; linseed oil meal, 12 per cent; crude casein, 3.7 per cent; alfalfa leaf meal, 1.5 per cent; table salt, 0.4 per cent; and calcium carbonate, 0.4 per cent, was fed daily. By adding one-half its weight of water, this diet was made into a paste that did not spill easily from the feed cups and the mice were able to gain weight on it.

Creatine and creatinine determinations were made by the technic of Folin (17) modified for the Evelyn photoelectric colorimeter. Estrogens and 17-ketosteroids were extracted from the urine after the technic of Smith and Smith (31). They were then separated from each other by the method of Gallagher and his associates (18). The 17-ketosteroids were measured colorimetrically by a modification of the Zimmerman reaction. Estrogens were measured by assay on castrated mice, and determinations were made on both an aliquot of the total benzene extract and on the NaOH-soluble fraction separated from the neutral fraction. These technics have previously been described in detail by Nathanson, Towne, and Aub (27). Estrogenic activity in mouse urine was checked

in 2 specimens by the use of Astwood's uterine weight technic (3). Zinc hydrolysis was carried out preliminary to extraction on 2 urine specimens by the method described by Smith and Smith (32).

Urines were collected over 24 hour periods on small groups of C3H and C57 males and females of various ages, and creatine-creatinine ratios determined on 87 of these specimens.

Table I summarizes the data obtained on the three groups. The average weight of the C57 mice rose slightly during the 4 to 10 month period, the virgin C3H mice remained unchanged, while the once-pregnant C3H mice showed a slight loss. It is therefore apparent that conditions within the cage did not permit entirely normal growth. The creatinine excretion in relation to body weight remained fairly constant from the fourth to eighth months of age, the C57 mice excreting an average of 15.6 mgm. the virgin C3H mice 18.7 mgm., and the once-pregnant C3H mice 19.7 mgm., per mouse per month. During the ninth and tenth months creatinine excretion was decreased in all groups. This may be due to less satisfactory urine collections resulting from a decreased urine volume due to the weight losses and death of some of the animals, although it is possible that the mice were excreting less creatinine. From the data obtained over the period of 4 to 8 months of age, however, it is calculated that the 20 gm. mouse excretes about 0.5 mgm. creatinine per day (25 mgm./kg.) and that no obvious strain difference exists.

TABLE I: WEIGHT, URINE EXCRETION, CREATININE, 17-KETOSTEROID, AND ESTROGEN EXCRETION IN VIRGIN C57 AND C3H AND ONCE-PREGNANT C3H FEMALE MICE OVER THE AGE PERIOD OF 4 TO 10 MONTHS

Urinary creatinine excretion expressed as mgm. per mouse per month. 17-Ketosteroids expressed as mgm. per mouse per month, and as mgm. per 10 mgm. creatinine in the urine. Estrogens, expressed in international units, calculated per mouse per month and also per 10 mgm. creatinine in the urine.

Strain	Age, months	Number of mice per group	Average weight per mouse, gm.	Urine excretion per mouse per month, cc.	Creatinine excretion per mouse per month, mgm.	17-Ketosteroids, Excretion per mouse per month, mgm.	17-Ketosteroids, Excretion per 10 mgm. creatinine, mgm.	Estrogens, international units, Excretion per mouse per month	Estrogens, international units, Excretion per 10 mgm. creatinine
C57(V) *	4	24	19.0	23.1	12.7	0.68	0.54	1.9	1.5
C3H(V)	4	24	21.6	46.2	18.2	0.86	0.47	1.8	1.0
C57(V)	5	24	20.2	17.7	16.4	0.79	0.48	1.5	0.9
C3H(V)	5	24	22.2	35.3	21.2	0.87	0.41	2.3	1.6
C57(V)	6	24	21.1	15.8	17.4	1.40	0.88	1.7	1.1
C3H(V)	6	24	23.5	24.6	18.8	1.93	1.05	1.2	0.7
C3H(P) †	6	24	26.2	29.0	21.4	0.46	0.22	2.3	1.1
C57(V)	7	22	21.1	10.0	16.4	1.13	0.65	2.2	1.4
C3H(V)	7	24	23.6	17.5	18.4	1.00	0.55	1.2	0.6
C3H(P)	7	24	25.1	21.4	21.4	1.23	0.63	1.4	0.7
C57(V)	8	21	21.5	18.5	15.1	1.10	0.72	2.1	1.4
C3H(V)	8	24	23.5	19.6	16.7	1.67	1.00	1.4	0.8
C3H(P)	8	23 [1]	25.6	20.3	16.4	0.88	0.53	1.2	0.8
C57(V)	9	19	20.4		9.3	0.75	0.94	2.6	3.3
C3H(V)	9	24	22.6		15.2	1.29	0.85	1.8	1.2
C3H(P)	9	19 [2]	23.9		12.7	0.82	0.65	2.3	1.8
C57(V)	10	13	22.0		9.2	0.67	0.73	3.3	3.6
C3H(V)	10	23 [3]	20.8		12.4	0.55	0.44	2.1	1.7
C3H(P)	10	18 [2]	23.1		8.1	0.70	0.87	2.7	3.3
C57(V)	Average for	21	20.7	15.0	13.8	0.93	0.71	2.2	1.9
C3H(V)	entire period	24	22.5	30.4	17.3	1.17	0.68	1.7	1.1
C3H(P)		22	24.8	23.6	16.0	0.82	0.58	2.0	1.6

* V = Virgin.
† P = Postpartum.
[1] 1 dead with a spontaneous mammary tumor.
[2] 4 dead with spontaneous mammary tumors.
[3] 1 dead with a spontaneous mammary tumor.

RESULTS

Several general observations between the 2 strains were noted. Low tumor strain mice (C57) had a lesser food and water intake and urine excretion as compared with the C3H strain. During the winter, the urine excretion of all strains decreased (Table I). The C57 mice had a higher mortality rate: Nine out of 22 mice died between the ages of 9 and 11 months. Those available for autopsy had liver or kidney infections. The once-pregnant C3H mice developed only 4 of 22, and the virgin C3H mice 1 of 24 spontaneous mammary tumors at 11 months of age. This is lower than the incidence in our colony, but may be partially explained by their abnormal living conditions and a probable decrease in food intake (37).

Substances present in the neutral fraction of the ben-

zene extract of mouse urine react with *m*-dinitrobenzene in an alcoholic alkaline solution (Zimmerman reaction) to produce a color similar to, but not identical with, that obtained in corresponding fractions of human urine (23, 28, 36). Neutral extracts of human urine are known to contain ketonic and non-ketonic substances. The ketonic fraction includes the 17-ketosteroids. Although the non-ketonic fraction does not give the Zimmerman reaction, it contributes to the color when the crude extract is assayed. By treatment with Girard's reagent T, the ketonic substances may be separated. Thus assay of this ketonic fraction alone will eliminate partially, if not completely, the additional chromogen from the non-ketonic material present in the crude extract. It seemed possible that non-ketonic substances might explain the differences in reaction between mouse and human extracts. Accordingly, various mouse urine extracts were treated with Girard's reagent T. It was found that the crude mouse urine extracts contained both ketonic and non-ketonic substances, with ratios analogous to those obtained in human extracts. However, by employment of the Zimmerman reaction, it was not established that the ketonic fraction was identical with that of human urine, since the mouse urine extract did not give exactly the same color. This does not rule out the presence of 17-ketosteroids in mouse urine, but it is possible that other ketonic substances, non-steroid as well as other ketosteroids, may be present. These may be entirely responsible for, or may add to or mask, the typical color of the 17-ketosteroids. A similar situation exists to some extent in human urine. The ketonic material obtained in the mouse urine has not been identified further. However, because of the similarity in reaction, the material assayed in the mouse urine is referred to as 17-ketosteroid-like. The excretion levels of the 17-ketosteroid-like substances, measured in androsterone equivalents, varied from month to month in each group (Table I). In general, when calculated in terms of excretion per mouse per month, the levels for the C3H virgin females are somewhat higher than in the other two groups. However, when the excretion rate is calculated per 10 mgm. of creatinine in the urine, there is no appreciable difference in the groups. The highest levels are found between the sixth and ninth months. Assays of the material by the Holtorff-Koch technic gave values about 50 per cent lower than the modified Oesting method (23). This has been observed likewise in human urine. In the light of obvious difficulties in collection and analysis, one is forced to conclude that the differences in the various groups are not significant.

In contrast to the shortcomings in the assay and identification of the 17-ketosteroid-like substances, less difficulty was encountered in establishing the presence of estrogenic activity in the urine. The collection time was sufficiently long to equalize the normal variations that occur in the estrous cycle. However, the inherent errors in most methods of bioassay and the difficulties in assaying accurately small quantities of estrogens are sufficiently great so that only fairly large variations in output should be considered significant. Injection of the extracts produced typical smears of cornified vaginal epithelium in castrated mice (Allen-Doisy technic), and considerable increase in uterine weight, up to 50 per cent, occurred in 21 day old female rats 6 hours after injection (Astwood technic). In most cases, both the crude benzene extracts and the NaOH-soluble (phenolic) fraction of these extracts containing the estrogens, were assayed on each urine specimen. The latter gave values about one-third lower, but the two types of extracts paralleled each other closely. The data reported in Table I represent the determinations on the crude benzene extract, since it was desired to estimate the total estrogenic activity. Zinc hydrolysis did not perceptibly alter the estrogenic activity of mouse urine (Table II).

TABLE II: EFFECT OF ZINC-HYDROCHLORIC ACID HYDROLYSIS ON ESTROGENIC ACTIVITY OF MOUSE URINE

Pooled specimens, untimed collection

Group No.	Strain	Hydrolysis	Estrogenic activity (international units)
102A	C57	HCl	28
102B	C57	Zn-HCl	24
111A	C57	HCl	32
111B	C57	Zn-HCl	26
103A	C3H	HCl	30
103B	C3H	Zn-HCl	22
112A	C3H	HCl	24
112B	C3H	Zn-HCl	26

Data are calculated on the basis of the excretion rate per mouse per month and per 10 mgm. of creatinine in the urine. In the C3H virgin female there is no demonstrable evidence of alteration of estrogen excretion. The excretion levels in the C57 virgin females and in the C3H once-pregnant mice tend to rise with an increase in age.

There is a suggestion, from the data in Table I, and further confirmed by subsequent studies on mouse urine, that the low tumor C57 strain excrete slightly more estrogens than the high tumor C3H strain. The degree of difference is variable, but almost always present, as tested by both the vaginal smear and uterine weight technic. The C57 mice seem to excrete an average of 30 per cent more estrogen than the C3H mice. However, in view of the small quantity of excreted estrogens and the variations to be expected in the technic of bioassay this difference is not considered to be of significance. A previous pregnancy appears

to increase slightly the estrogen excretion in strain C3H.

Male and female C3H and C57 mice excrete large quantities of creatine and this appears to be related to their basic physiology, since sexual maturity in the male does not notably decrease the rate of creatine excretion as compared to the female. The creatinine-creatine ratios were very variable within the same group, as evidenced by the large standard deviation; so only tentative conclusions can be drawn. The C3H or C57 females had similar creatine-creatinine ratios until they were 10 to 12 months old. Thereafter, creatine excretion increased in the C57 females and decreased in the C3H females. The C57 males appeared to excrete more creatine than the C3H males, and this difference remained throughout the whole period of observation (Table III).

TABLE III: RATIO OF CREATININE : CREATINE EXCRETION AT VARIOUS AGES IN MALE AND FEMALE C57 AND C3H MICE

Age of mice, mos.	Ratio of creatinine : creatine with standard deviation per group			
	C57 Female	C3H Female	C57 Male	C3H Male
2-5	(5) *	(7)	(6)	(11)
	1:0.70 ± 0.21	1:0.80 ± 0.29	1:0.91 ± 0.34	1:0.65 ± 0.30
6-9	(10)	(9)	(8)	(4)
	1:0.74 ± 0.09	1:0.78 ± 0.08	1:0.75 ± 0.22	1:0.46 ± 0.13
10-12	(8)	(5)	(8)	(6)
	1:0.92 ± 0.33	1:0.53 ± 0.14	1:0.71 ± 0.27	1:0.51 ± 0.12
Average	(23)	(21)	(22)	(21)
	1:0.79 ± 0.23	1:0.71 ± 0.16	1:0.78 ± 0.27	1:0.57 ± 0.25

* Figures in parentheses represent number of samples per group.

DISCUSSION

The presence of estrogenic and 17-ketosteroid-like substances in the urine of normal female mice is reported.[1] Similar observations have been recorded in rats. Four rat units (about 34 international units) per liter have been found in female rat urine, and this rose to 17 rat units per liter during pregnancy (4). Lampton and Miller (24) recovered 1.5 color units of 17-ketosteroid in the daily urine excretion of the male rat (equivalent to 0.14 mgm. androsterone) as measured by the Oesting colorimeter. These results in the rat are within the range of our findings of 30 to 150 international units of estrogen per liter of mouse urine, and 1.45 mgm. of 17-ketosteroid-like substances excreted per kgm. of mouse per day, as compared to about 0.70 mgm. per kgm. of rat per day. According to Parfentjev and Perlzweig (29) adult male white mouse urine contains 0.1 per cent creatinine and 0.09 per cent creatine. Assuming that the mouse excretes 0.5 to 1.0 cc. urine per day, this would equal 0.5 to 1.0 mgm. creatinine per day, and the creatinine-creatine ratio of 1:0.9 corresponds with our data.

Our observations indicate that the C57 female mouse excretes slightly but not significantly more estrogenic material than the C3H. Therefore these data on excretion rates of naturally occurring estrogens have produced no evidence that accounts for the difference in the incidence of mammary tumors in these mice.

Correlating these conclusions with other reports on the sex physiology of high and low tumor strains of mice must be done with caution. The steroid hormones extracted from the urine are the end result of a complicated metabolic cycle involving their formation, secretion, uptake by other organs, utilization, conversion into more or less biologically active substances, and, finally, destruction or excretion. The forms in which the steroids are excreted in the urine vary as to chemical structure and biologic activity. In our studies we measured the gross biologic activity of estrogens in the urine, and the quantity of a compound in the neutral fractions of benzene extracts of the urine that gave a color resembling the Zimmerman reaction in similar human urinary extracts. Only if the urinary excretion of these substances revealed great differences between the C57 and C3H mice could any inference be drawn as to the rate of formation or metabolism of these substances in each strain. Since the excretion of estrogens and 17-ketosteroid-like substances were not greatly different in the two strains, further attempts at finding significant strain differences in the urine will necessitate a qualitative and quantitative analysis of the different chemical forms of

[1] Since this paper was submitted for publication the presence of estrogenic material in the phenolic fraction of an extract of the urine of mice of the same order of magnitude as that published here has been reported (DORFMAN, R. I., and GARDNER, W. U. Metabolism of the Steroid Hormones. The Excretion of Estrogenic Material by Ovariectomized Mice Bearing Adrenal Tumors. Endocrinology, **34**:421-423. 1944).

these steroids, and the identification of the substances giving the Zimmerman reaction.

At present there is no conclusive evidence that the high mammary tumor strain mice form and metabolize estrogens differently from low tumor strains (40), and our observations are in keeping with others. It would seem fairly evident from the data available that the estrogens are essential for the growth of the mammary gland, and that they are carcinogenic only in that they bring the gland to a sufficient state of differentiation for it to evince its tumor susceptibility. Metabolic differences that have been described between strains have also failed to throw any direct light on the basis of tumor formation. That the mammary glands of low tumor mice do not respond as completely as those of high mammary tumor strains to estrogens (22), and that these differences in response are related to exposure to the milk-factor of Bittner (41) are the most significant points of difference yet encountered.

SUMMARY AND CONCLUSIONS

Metabolic differences between high and low tumor strains of mice and between litters of high and low tumor strain mice foster-nursed by the reciprocal mother are reviewed.

Comparative observations were made on C57 (low tumor strain) virgin and C3H (high mammary tumor strain) virgin and once-pregnant female mice. The C3H required more food than the C57 mice to maintain body weight. Both strains excreted approximately 0.5 mgm. creatinine per 20 gm. mouse per day.

The males and females of both strains excreted relatively large quantities of creatine in their urine. The creatine-creatinine ratio in the C57 and C3H females were similar until the tenth to twelfth months of age, when the creatine output rose in the C57 and fell in the C3H strain mice. The C57 male mice consistently excreted more creatine that the C3H males.

Each mouse excreted in its urine an average of 1.2 to 3.3 international units of estrogens a month. The C57 mice appeared to excrete on the average slightly more estrogenic material (30 per cent) than the C3H mice, but the difference is not considered significant. Both strains excreted 0.46 to 1.93 mgm. of a 17-ketosteroid-like substance per mouse per month with no appreciable strain differences.

Therefore, judged from urinary excretion rates, there is as yet no evidence that high mammary tumor strain mice form or metabolize estrogens or 17-ketosteroid-like material in any significantly different fashion from a low tumor strain. Estrogens are to be regarded as an essential but not a specifically carcinogenic factor in the development of spontaneous mammary tumors in mice.

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The Genetics and Linkage Relationship of the Inherited Susceptibility to Mammary Cancer in Mice*

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Studies on the etiology of mammary cancer in mice may be divided into two groups: (a) Those made on heterozygous animals, and (b) Those made on inbred strains and their reciprocal hybrids. Haldane (11) stated that exact work is impossible unless homozygous animals are used, because no two individuals might have the same genetic constitution when other types of animals were tested and the results might not be the same in various experiments. Moreover, other conditions must also be controlled in order to obtain reliable data.

While a great amount of our knowledge concerning the problem of cancer may be attributed directly or indirectly to the use of "pure" strains of mice, some strains have diverged into sublines that may differ genetically from one another sufficiently to be considered as distinct strains [Andervont (2), Bittner (7, and unpublished data)]. Thus all experimental and control animals should be representatives of the same line and should be observed in the same laboratory during the same period.

The early studies of Bashford, J. A. Murray, Tyzzer, Haaland, Slye, and Lathrop and Loeb were of importance because they established the fact that some lines or families of mice produced more tumors than did others, and indicated a genetic transmission of the disease; for references see Loeb (22) and Little (13).

By studying the incidence in hybrids Lathrop and Loeb (18-20) could find no explanation that would account for the results in all the reciprocal crosses. In some hybrids the higher rate of the maternal strain predominated; in others the hybrids showed the high incidence characteristic of the paternal line. Although their results suggested that the maternal strain may possibly be of greater importance, they believed that there might be a partial linkage of the factors determining tumor incidence with the sex determinants. Later Loeb (21) and Tureen and Loeb (24) assumed that two sets of factors controlled the tumor rate and the tumor age and that it was possible to dissociate these two sets, especially through hybridization. However, in 1940, Loeb (22) stated that "The so-called 'spontaneous' mammary-gland carcinoma is a cancer produced by the estrogen given off rhythmically in mice hereditarily predisposed to this disease." Of more significance were the observations of Lathrop and Loeb (18-20) on the role of the estrogenic hormones in the genesis of mammary cancer in mice.

Following the discovery of the maternal influence in the etiology of these tumors, various theories were advanced on how it might function and on its importance (12, 15-17), but foster-nursing experiments demonstrated that it is transferred in the milk (4, 9). Following the foster nursing of inbred strains and their reciprocal hybrids, the role of inherited susceptibility was again evident. In one cross the observations were in accord with the genetic theory that the susceptibility for mammary cancer is transmitted as a single dominant factor, but other explanations were possible (5, 6, 8, 10). Andervont (1) suggested "that genetic factors exert their influence in the occurrence of spontaneous mammary cancer in mice by controlling the degree of susceptibility of the animal or the concentration of the extrachromosomal, or milk influence," but that in some crosses the paternal parents introduced factors that influenced the incidence of cancer in the progeny (3).

Thus, from the data now available, three "inciting" influences have been recognized in the production of mammary cancer in mice: the agent transferred in the milk, a dominant inherited susceptibility, and the estrogenic and associated hormones. The possible relationship of these causative influences has been discussed previously (9).

In this report we wish to consider the possible linkage relationship between one of the factors for the inherited susceptibility for spontaneous mammary cancer and one of the genes controlling coat color in mice.

MATERIALS AND METHODS

The two inbred strains used in these experiments were the B (C57 black) and the A stocks.

* These experiments were started at the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, and were assisted by grants from the National Cancer Institute and The Jane Coffin Childs Memorial Fund for Medical Research.

Less than 1 per cent of the breeding females of the B stock have spontaneous mammary cancer in the end (14). Several sublines of this strain are being carried that trace back to single pairs brought from Ann Arbor, Michigan, to Bar Harbor, Maine, in 1929. None of the breeding females of the B strain serving as controls in this experiment developed mammary tumors (10.)

Approximately 95 per cent of the breeding females of the inbred A strain ultimately have mammary tumors (10). Sublines of the A cancerous strain have not been maintained; the strain has been inbred for more than 70 generations by brother-to-sister matings, and over 40 consecutive generations of mammary tumors have been recorded.

In this report only the hybrids that were nursed by females of the cancerous A stock are included. Those that did not receive the mammary tumor milk inciter had a low incidence of tumors, and are of little value in a discussion of the inherited susceptibility for mammary cancer (5, 10).

The hybrids that had maternal parents from the A strain and paternal parents from the B stock, and nursed A females, were called ABF_1 by A. The hybrids made by reciprocal matings ($B \times A$) were termed BAF_1. Because they were transferred to females of the A stock soon after birth, they are designated as BAF_1 by A. The hybrids of the F_1 generations were mated *inter se* to produce the F_2 hybrids, etc. With the exception of the BAF_1 by A mice, all hybrids nursed their maternal parents but are designated by the strain used to nurse the F_1 animals (10).

Two groups of backcross generation hybrids are also considered that were produced by mating either ABF_1 by A or ABF_2 by A females to males of the B stock. These were called BBC ("B" backcross) animals.

To secure the experimental animals of the hybrid generations, only a small number of mothers was used and as many progeny as possible were continued from each one. The mice of the reciprocal generations were studied during the same period. All the females were continued as breeders and they were permitted to nurse their progeny.

The animals received Purina fox chow and an unlimited amount of water.

Only carcinoma of the mammary glands is considered in this report. The incidence was determined by the percentage of mice in each group living beyond the age at which the earliest tumor was observed.

All animals of the A stock, F_1 and F_2 hybrid and F_1 backcross generations had cancerous mothers; mice of the F_3 hybrid and F_2 backcross generations had either cancerous or noncancerous mothers.

TABLE I: DATA FOR THE TOTAL NUMBER OF RECIPROCAL HYBRIDS BETWEEN THE CANCEROUS A AND LOW CANCER B STOCKS NURSED BY FEMALES OF THE A STOCK

All had cancerous mothers except as noted. The difference in incidence for the total number of F_1 by A, and A by A was 2.74% ± 1.50 or 1.83 × S. E.

Stock	No.	Ca.	% Ca.	Average age Ca.	Average age Non-ca.	Standard error of difference
A by A	972	924	95.1	286	426	
B by B	275	0	0.0	. . .	489	
ABF_1 by A	123	116	94.4	336	369	1.21 × S. E.
BAF_1 by A	111	100	90.1	346	568	
Total F_1 by A	234	216	92.3	341	490	
ABF_2 by A	277	214	77.3	397	535	1.65 × S. E.
BAF_2 by A	114	79	69.3	452	632	
Total F_2 by A	391	293	74.9	412	570	
ABF_3 by A	339	227	67.0	378	545	0.30 × S. E.
BAF_3 by A	278	183	65.8	388	577	
Total F_3 by A:						
Cancer F_2 mothers	508	360	70.9	380	557	5.02 × S. E.
Non-ca. F_2 mothers	109	50	45.9	401	565	
Total	617	410	66.5	383	559	
ABF_1 by A—BBC	311	187	60.1	426	626	
ABF_2 by A—BBC:						
Cancer F_2 mothers	223	140	62.8	435	637	7.95 × S. E.
Non-ca. F_2 mothers	60	3	5.0	480	715	
Total	283	143	50.5	437	679	

EXPERIMENTAL RESULTS

The incidence of mammary cancer in mice of the inbred strains and their hybrids is given in Table I,

with the average ages expressed in days. No significant difference was encountered for the incidence in any of the reciprocal groups, which permits the totaling of the mice of the respective generations. Likewise, the variation in the incidence of cancer for the mice of the A stock and the total number of F_1 by A hybrids was not of statistical significance ($1.83 \times$ S. E.). There were, however, differences in the average ages at which the mice of these classes developed cancer.

If there is an inherited susceptibility to mammary cancer in mice, the segregation of this factor (or factors) should be evident in mice of the second hybrid generation. Whereas the incidence in mice of the F_1 generation was 92.3 per cent, that for mice of the F_2 generation was 74.9 per cent, which would be in accord with the genetic theory that the inherited susceptibility might be transmitted as a single dominant factor.

The total F_2 by A population had an incidence of 66.5 per cent; the incidence for mice with cancerous mothers was 70.9 per cent, whereas those with noncancerous mothers had an incidence of 45.9 per cent ($5.02 \times$ S. E.).

Hybrids of the ABF_1 backcross generation had an incidence of 60.1 per cent, and mice of the ABF_2 backcross generation an incidence of 50.5 per cent. Cancerous and noncancerous females were used to produce the ABF_2-BBC hybrids. Those with cancerous mothers had an incidence of 62.8 per cent, while the progeny of noncancerous mothers had an incidence of 5.0 per cent.

Mice of the A strain are albino in coat color and carry the brown factor, while the animals of the B stock are black. The expected ratios in the F_2 generation would be 9 black : 3 brown : 4 albino mice. The relationship between the coat color of the F_2 by A hybrids and the incidence of mammary cancer is presented in Table II.

Brown mice of the F_2 by A generation were observed to have a higher incidence (88.1 per cent) of cancer than did the albino (76.5 per cent) and black (68.9 per cent) animals. Comparisons showed that the variations between the browns and mice of other coat colors were probably significant.

The mice of the ABF_2 by A—BBC generation had mothers with various coat colors (all BBC animals were black). The offspring of brown cancerous mothers had a higher incidence (68.2 per cent) than did those having black (59.6 per cent) or albino (55.4 per cent) cancerous mothers. With the number of mice studied, these differences were not significant. All the F_2 by A brown mice used to produce hybrids of the ABF_2 by A—BBC generation died cancerous, but some albino and black F_2 by A mothers died noncancerous. When their progeny were grouped with those of cancerous females with like coat colors, significant differences were found (Table III) between the progeny of the brown and black mothers ($4.77 \times$ S. E.), and the brown and albino mothers ($3.19 \times$ S. E.), but not for the black and albino mothers ($1.30 \times$ S. E.).

An analysis of the F_3 by A data from the standpoint of linkage was made difficult because in certain matings it was not possible to determine what factors for coat color were transmitted by the parents of the second hybrid generation. Many of the matings were between albino animals, and these parents might

TABLE II: INCIDENCE OF MAMMARY CANCER IN THE F_2 BY A GROUP WHEN MICE ARE TABULATED BY COAT COLOR

Total F_2 by A:	No.	% Ca.	Difference between incidences:
Brown	84	88.1	Br. and Blk.: $19.2\% \pm 5.6$ or $3.4 \times$ S. E.
Black	209	68.9	Br. and Al.: $11.6\% \pm 5.7$ or $2.0 \times$ S. E.
Albino	98	76.5	Blk. and Al.: $7.6\% \pm 5.5$ or $1.2 \times$ S. E.
Total	391	74.9	

TABLE III: INCIDENCE OF MAMMARY CANCER IN THE ABF_2 BY A—BBC (ABF_2 BY A♀♀ × B♂♂) HYBRIDS ACCORDING TO COAT COLOR AND WHETHER OR NOT THE ABF_2 BY A MOTHERS DIED OF CANCER

ABF_2 by A mothers	Cancerous mothers		Noncancerous mothers		Total	
	No.	% Ca.	No.	% Ca.	No.	% Ca.
Brown	110	68.2	0	. . .	110	68.2
Black	57	59.6	40	0.0	97	35.1
Albino	56	55.4	20	15.0	76	44.7
Total	223	62.8	60	5.0	283	50.5

Differences in incidence

Br. and Blk. Mothers: $33.1\% \pm 7.0$ or $4.8 \times$ S. E.
Br. and Al. Mothers: $23.5\% \pm 7.4$ or $3.2 \times$ S. E.
Al. and Blk. Mothers: $9.7\% \pm 7.5$ or $1.3 \times$ S. E.

have carried black and/or brown. However, mice born of brown parents had an incidence of 77.5 per cent, while other mice with cancerous mothers had an incidence of 70.3 per cent.

Of interest were the results obtained from mating 5 F_2 by A females to the F_2 by A black male, No. 65280 (Table IV). Three of the females (2 brown and 1 black) died cancerous and their progeny showed a high incidence of cancer for mice of the F_3 generation. One brown noncancerous female had progeny with an incidence of 13 per cent, while the progeny of a noncancerous black female had an incidence of 32 per cent. If the progeny born to the noncancerous brown female are not included, the incidence for the other progeny of the black male, No. 65289, was: 33 blacks, 48.5 per cent; 13 browns, 76.9 per cent; and 15 albinos, 66.7 per cent. Again we note a higher incidence among the brown mice, but the differences are not significant because of the small numbers.

From the incidence of mammary cancer observed in the various hybrid generations in this study, a single dominant factor could reasonably explain the transmission of the inherited susceptibility. In most groups, either the incidence was in accord with this hypothesis or more tumors were recorded than would be expected. If, however, the incidence was considered according to the coat color of the mice of the F_2 by A generation, the theory for a single factor would not apply, as more brown mice had tumors than would be expected with independent assortment, but the incidence for the brown mice was lower than would be expected for linkage. Thus other theories must be considered to explain the results.

It will be recalled that 18.4 per cent of the mice of the C57 black strain with the active milk agent died cancerous but none of the mice of this stock that did not have this agent developed tumors. If animals of this strain (mice of several sublines were probably

TABLE IV: INCIDENCE OF MAMMARY CANCER IN THE PROGENY OF ONE BAF_2 BY A BLACK MALE WHEN MATED TO CANCEROUS (+) OR NONCANCEROUS (—) BAF_2 BY A FEMALES

		Total progeny		Coat color of progeny					
				Black		Brown		Albino	
BAF_2 by A♀♀:	Diag.	No.	% Ca.	No.	% Ca.	No.	% Ca.	No.	% Ca.
63355 Brown	+ 379	16	81	5	80	6	83	5	80
63503 Brown	+ 474	10	70	6	83	4	50	0	
63504 Albino	+ 358	10	80	3	33	3	100	4	100
63354 Brown	— 780	15	13	7	0	8	25	0	
63356 Black	— 423	25	32	19	32	0		6	33

Females mated to BAF_2 by A black male, No. 65280

DISCUSSION

An analysis of the genetic susceptibility for spontaneous mammary cancer in these experimental data, obtained by crossing mice of a cancerous and a low-cancer stock, was made difficult because:

A. As previously reported (10), 18.4 per cent of the mice of the low cancer strain developed mammary cancer following foster nursing by females of the same cancerous strain. This would indicate that if the mice of the resistant stock were genetically nonsusceptible, the inciting influences of the milk agent and the hormones were sufficient to overcome the threshold of nonsusceptibility in some animals and produce tumors. It would also follow that some of the cancerous hybrids were probably genetically low cancerous.

B. The incidence of spontaneous cancer varied in many groups with the age at which the mothers became cancerous. Some of the differences encountered, for instance in the F_2 by A hybrids, were of statistical significance.

C. Many of the hybrids born in the third and following litters showed higher incidences than did the mice of the same groups born in the first and second litters.

included in our data) were not susceptible to mammary cancer, these mice would be genetically low cancerous but somatically cancerous. If this was the case, it would also be assumed that some of the nonsusceptible mice of the hybrid generations also died cancerous. The observed incidence for cancer would then include not only animals that had the inherited susceptibility but also those that developed tumors because of other inciting influences. These findings would tend to show that the inherited susceptibility to mammary cancer might be transmitted by multiple factors. Also corroborating this view was the fact that some brown females of the F_2 by A generation died noncancerous and apparently did not transmit the inherited susceptibility to their progeny. However, the ratios based on two dominant factors and corrected on this basis (18.4 per cent of the nonsusceptible mice developing cancer) were lower than the observed data.

When two dominant factors are transmitted, a certain number of the hybrids would carry one of the factors, either in the homozygous or heterozygous condition, but have the recessive alleles of the other. If we assume that the mice of the C57 black stock did not have any of the susceptibility factors, it might be

possible that the hybrids with one of the susceptibility factors would have a higher incidence than the fostered B mice. This figure would also have to take into consideration the difference in the incidence for mice born to mothers that developed tumors at various ages and for those born in succeeding litters.

With these assumptions, it would be possible to explain the data on the basis that the inherited susceptibility for mammary cancer in mice is transmitted by multiple factors, one of which is linked with the brown gene.

Before the number of factors can be determined it will be necessary to evaluate further the roles of extrinsic and metabolic influences in the development of mammary cancer in mice. These may be determined in part by the genetic constitution of the individual. That is, if multiple factors are transmitted, the mice without any of these factors might be expected to have a greater "threshold" to overcome, by the action of the milk agent and the estrogenic hormones, than would animals that had one or more of the susceptibility factors. Other genetic factors may operate in the development of mammary cancer that are not associated with the inherited susceptibility.

Although most mammary tumors in mice result from the combined inciting influences of the inherited susceptibility, the estrogenic hormones, and the milk agent, they do develop in some animals that have not all these mammary tumor inciters. Other influences may be involved that have not been recognized. Because of these facts it has not been possible, in these experiments, to determine definitely the number of genetic factors characteristic of the inherited susceptibility to mammary cancer.

CONCLUSIONS

Reciprocal F_1 hybrids produced by mating mice of one low cancer (C57 black) and one high cancer (A) strain and nursed by females of the cancerous stock gave, in breeding females, approximately the same incidence of spontaneous mammary cancer.

No evidence was secured to suggest any intrauterine influence for the development of mammary cancer in mice.

The incidence in the total number of F_1 hybrids nursed by females of the A stock did not differ significantly from the incidence secured in mice of the cancerous A stock.

Although the pooled data obtained in all the hybrid generations could be accounted for on the genetic theory that the inherited susceptibility for mammary cancer in this cross was transmitted as a single dominant factor, it becomes evident on analysis of the incidence of cancer in the several subgroups that such a simple interpretation is inadequate and that other factors are probably involved. Detailed analysis shows:

1. That the incidence of mammary carcinoma in the F_2 hybrids with brown coat color was significantly higher than in their litter mates with black or albino coats.

2. That not all brown mice became cancerous, nor was the incidence in brown mice as high as in mice of the high cancerous A stock.

3. The progeny of brown mothers had a higher incidence than did the progeny of black or albino mothers, but not all brown mothers transmitted the inherited susceptibility to their progeny.

4. The incidence of cancer was significantly greater, in some groups, in the mice born in the third and later litters than in mice born in the earlier litters from the same mothers.

5. The incidence in the progeny was influenced also by the age at which the mothers developed mammary cancer.

It has previously been shown that a considerable proportion of mice of the so-called nonsusceptible stock developed mammary cancer when given the active milk agent. Therefore even mice of these strains are not totally resistant, and either they must possess certain factors conducive to mammary carcinoma production, or the tumors must result from extrinsic and/or metabolic inciting influences. Obviously the mice of low cancer strains do not have all the inciting factors that are present in mice of the high cancer strains.

If some mice of a genetically nonsusceptible strain develop mammary cancer, it is probable that some cancerous hybrid animals are likewise nonsusceptible. Thus the incidence would not represent the true percentage of susceptible animals, and should not serve as the only basis for a genetic interpretation of the data.

It is concluded that the inherited susceptibility for spontaneous mammary cancer in mice, as transmitted by mice of the cancerous A stock, probably depends upon multiple genetic factors, one of which may be linked with the gene for brown coat color.

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Metabolic Studies in Mouse Leukemia

II. Metabolism of Livers of Mice with Lymphoid Leukemia*

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In mice with lymphoid leukemia malignant lymphocytes are found in large numbers not only in the lymphoid structures but also in other organs, notably the liver. Is the metabolic activity of these cells different in the two tissue environments? Does the presence of such cells in the liver affect the metabolism of the parenchymal cells? The first paper of this series (9) presented data on the metabolism of the leukemic lymph nodes. This paper presents a partial answer to the questions just stated. The importance of such studies in revealing the nature of leukemic and preleukemic changes in metabolism has recently been stressed by Burk and his associates (4).

METHODS

The oxygen consumption and aerobic and anaerobic glycolysis rates of excised liver slices were determined by the Warburg method in the manner described in detail in a previous paper (9).

The results obtained from the metabolic study of the liver are difficult to interpret, since the slices studied in the manometer vessels consisted not only of the malignant lymphocytes but also of liver parenchymal cells and occasionally of significant quantities of other tissues. To permit more meaningful calculations, the relative volumes of these components were estimated subjectively from a study of histological preparations of the livers. All microscopic examinations of the sections were made by Dr. Jacob Furth. The estimates are only approximate. The systematic relationships reported herein were not suspected at the time of the microscopic study.

RESULTS AND DISCUSSION

I. Metabolism of Normal Liver Tissue

The data obtained on the livers of 11 normal mice of stock Ak are shown in Table I. The average values, together with those of the few investigators who have studied mouse liver tissue, are as follows:

Table I: Detailed Data on the Metabolism of Normal Livers

Mouse number	Q_{O_2}	$Q_G^{O_2}$	$Q_G^{N_2}$	R. Q.
Ak(25)	3.19	1.52	— 0.16	...
Ak(42)	2.56	0.78	0.31	...
Ak(54)	5.49	1.26	0.68	0.70
Ak(55)	3.24	0.52	0.37	0.83
Ak555	5.54	1.10	...	...
Ak617	3.14	...	...	0.63
Ak635	2.77	— 0.68	— 0.89	0.85
Ak644	2.35	0.21	0.42	0.61
Ak645	1.88	1.62	...	...
Ak648	1.99	— 0.10	...	...
Ak656	1.73	...	...	0.88
Averages	3.09	0.68	0.05	0.75

Authors	Medium	Q_{O_2}	$Q_G^{O_2}$	$Q_G^{N_2}$
Hall	Ringer-phosphate $M/150$	3.09	0.68	0.05
Büngeler (2)	"Ringer"	11.51	0.46	2.28
Kodama (11)	"Bicarbonate"	12.3	...	...
Burk *et al.* (4)	Ringer-bicarbonate	1.5	0.42	0.25
Fuhrman (8)	Ringer-phosphate $M/100$	8.13	...	...

The average value for oxygen consumption is lower than those reported by the others who have investigated mouse liver (with the exception of Burk, who made four consistent determinations on two groups of animals). (In the rat there is also considerable discrepancy in the values obtained by different workers, the Q_{O_2}'s varying from 5.8 [Spirtes, 15] to 11.3 [Rosenthal and Lasnitzki, 14].)

The reason for the low value obtained is not clear. Absence of bicarbonate from the medium in which phosphate serves as the buffer reduces the Q_{O_2} of certain tissues, according to Laser (12) and others. This may explain why Kodama's values are the highest. However, other reasons must be sought for the difference between the present low results and those of Fuhrman. The latter had found that the Q_{O_2} of normal

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rat liver varies with tissue slice thickness, the optimum being 6.21 when the slices were 0.57 mm. thick and the value falling off sharply on both sides of this optimum. Upon request Fuhrman studied normal mouse liver, using slices 0.57 mm. thick. His results lead to the suspicion that the freehand slicing employed in the present experiments yielded slices above the optimum thickness. However, since the leukemic mouse liver was studied by the same methods as the normal mouse liver, the figures are comparable.

The finding that the aerobic glycolysis rate is greater than the anaerobic glycolysis rate, *i.e.,* that the manometrically determined Pasteur effect is negative, is not new, similar relations appearing in the averages of Burk, Behrens, and Sugiura (3) and in some of the experiments of Rosenthal and Lasnitzki (14), all of whom were studying rat liver tissue, as well as in some of the abnormal mouse livers studied by Dickens and Weil-Malherbe (7).

II. Metabolism of Livers with Lymphoid Leukemic Infiltration

Table II gives for each mouse studied: (a) the percentage of liver volume estimated to be occupied by the infiltrating malignant lymphocytes; (b) the oxygen consumption, and aerobic and anaerobic glycolysis rates determined upon the liver tissue; and (c) the anaerobic glycolysis rate of that mouse's lymph nodes. The other values for the metabolism of the lymph nodes of the mice will be found in Table I of the first paper (9).

Oxygen consumption.—The oxygen consumption of leukemic liver tissue is invariably higher than the average value for normal liver. The average Q_{O_2} values are: normal liver, 3.09; leukemic liver, 4.68.

It must be admitted that the Q_{O_2} values given in this paper for normal liver are highly variable, and moreover, as stated above, are below the values obtained by Büngeler (2), Kodama (11), and Fuhrman (8). Accordingly, the difference between the normal and leukemic liver Q_{O_2} values may be exaggerated. However, the Q_{O_2} of leukemic liver might be expected to be high, since the malignant lymphocytes present in it consume oxygen at a rate about double that of the liver cells.

Results similar to those of the present paper were obtained by Burk and his associates. In various types of leukemic livers of mice, the average Q_{O_2} values ranged from 2.2 to 7.1, in contrast to their normal value of 1.5.

Aerobic glycolysis.—The average $Q_G^{O_2}$ of leukemic liver is 0.24, a value below that for normal liver, which is 0.68. This occurs in spite of the fact that the $Q_G^{O_2}$ of leukemic lymph nodes (the average for stock Ak being 3.56, that for stock RAk, 1.31) is higher than that of either normal or leukemic liver. Moreover, negative values for the observed $Q_G^{O_2}$ of leukemic liver were found in 15 of the 34 animals studied. The present data suggest that some factor is operating in leukemic liver tissue that reduces its rate of aerobic glycolysis below that to be expected from the metabolic behavior of its constituents.

Table II: Detailed Data on the Metabolism of Leukemic Livers

Mouse number	Percentage of infiltration	Liver metabolism			Lymph node * metabolism
		Q_{O_2}	$Q_G^{O_2}$	$Q_G^{N_2}$	Q_G^N
He390	50	5.23	0.00	3.97	7.37
He445	50	4.71	— 0.47	6.49	8.31
He849	50	4.76	— 0.89	4.50	7.22
Hf449	50	6.38	1.62	9.26	6.54
Akf108	44	4.18	1.26	5.07	6.85
Hg484	42.5	4.60	0.78	4.24	7.48
Akf174	40	4.81	— 0.16	4.97	9.52
Hf835	40	5.33	0.52	...	6.59
Akf113	33	...	...	4.92	...
Akh84	33	...	...	2.20	4.86
Aki114	33	4.13	1.41	3.45	16.32
F.Akh304	30	5.70	— 0.10	4.76	...
He391	30	3.45	0.63	4.39	10.09
Hg123	30	6.96	— 0.31	3.56	11.98
Hh406	30	3.40	1.41	2.09	11.66
He381	27.5	4.50	0.78	5.13	9.78
Hf922	27.5	4.55	— 0.26	1.99	...
Hf965	27.5	5.49	1.52	3.97	8.79
F.Aki217	25	...	0.00	2.77	...
He882	25	...	— 0.37	3.14	8.32
Hf925	25	...	— 1.10	1.67	7.01
Akh118	22	...	...	3.14	14.23
Aki115	20	2.46	1.67	3.87	11.51
He27	20	3.82	— 0.63	0.84	7.17
Hf921	20	5.02	— 0.21	4.13	5.02
Hf982	20	2.56	0.42	1.52	6.49
Akf85	15	5.54	0.73	1.88	10.36
He693	15	3.97	— 0.99	...	7.27
Akh213	13.5	4.29	— 0.78	1.46	3.61
He28	12.5	3.50	— 1.36	6.69	6.22
He449	10	5.65	0.94	...	10.67
Hf836	7.5	2.35	— 0.05	2.41	7.27
Akh225	5	5.13	...	3.61	5.75
Aki188	5	4.86	0.26	1.20	7.16
Hh42	5	5.39	0.52	1.26	8.99
Hg104	3	4.24	0.73	1.62	8.42
Ha21	0	4.39	0.95	0.26	6.01
He679	0	8.32	— 0.26	3.35	8.26
Averages		4.68	0.24	3.42	8.33

* From data in the first paper (9).

The results are not in agreement with those of Burk and his co-workers (2), in that the latter found a higher rate of aerobic glycolysis in livers of mice with various types of leukemia, the $Q_G^{O_2}$ values ranging from 0.87 to 1.9, than in normal liver with a $Q_G^{O_2}$ of 0.42. The relatively lower Q_{O_2} of normal livers found by Burk and

his group may account for the relatively higher $Q_G^{O_2}$ of their leukemic livers, compared with those studied by the present author.

Burk and his associates have thrown considerable light on the metabolic behavior of normal and leukemic liver with reference to acid production and removal by comparing the $Q_G^{O_2}$ obtained manometrically with the lactic acid changes determined by chemical analysis. In normal liver the manometric $Q_G^{O_2}$ was positive, but lactic acid decreased. In other words, the liver cells produced other acids faster than they removed lactic acid. However, in the leukemic livers they studied the infiltrating cells produced lactic acid faster than the liver cells could remove it.

The low $Q_G^{O_2}$ values in the livers that the present author has studied would, in terms of these concepts, require the operation of two factors. First, as originally suggested by Dr. E. Shorr, the lactic acid produced by the infiltrating malignant lymphocytes may be oxidized or otherwise utilized by the liver parenchymal cells. This, however, would not reduce the $Q_G^{O_2}$ below the level found in normal liver. Accordingly a second factor would be required, possibly either suppression of the production by the liver cells of acids other than lactic, or, alternatively, the utilization of such acids by the infiltrating cells. It would be, however, of small magnitude.

TABLE III: RELATION OF ANAEROBIC GLYCOLYSIS RATE OF LEUKEMIC LIVER TO THE DEGREE OF INFILTRATION BY MALIGNANT LYMPHOCYTES

Percentage of infiltration		Number of cases	$Q_G^{N_2}$		
Range	Average		Average	Minimum	Maximum
0	0	2	1.80	0.26	3.35
1-10	5	5	2.02	1.20	3.61
11-20	17	7	2.91	0.84	6.69
21-30	27	11	3.33	1.67	5.13
31-40	35	4	3.88	2.20	4.97
41-50	48	6	5.59	3.97	9.26

Anaerobic glycolysis.—The $Q_G^{N_2}$ of leukemic liver averages 3.42, which is much in excess of the normal liver average of 0.05. This finding is in agreement with that of Burk and his associates (4) on livers of mice with various types of leukemia.

We may first examine the relation between the liver $Q_G^{N_2}$ and the degree of infiltration by malignant lymphocytes; the pertinent data are given in Table III and Fig. 1. The regression equation for this relation, the line for which is included in the figure, has been calculated by the method of least squares and is:

$$Q_G^{N_2} = 1.50 + (.0773 \times \text{percentage infiltration})$$

Two relationships are brought out by this treatment of the data.

First, the $Q_G^{N_2}$ of the liver increases linearly with the degree of lymphocytic infiltration. This is to be expected, in view of the active anaerobic glycolysis carried on by the leukemic cells. On this basis we may estimate the $Q_G^{N_2}$ of the lymphocytes themselves by extrapolating the line to 100 per cent infiltration, which yields a value of 9.23. Now the lymph nodes are made up to a very large extent of leukemic lymphocytes, and so may be considered as approximating closely the condition of 100 per cent infiltration. The lymph nodes of the same mice from which the liver samples were obtained had an average $Q_G^{N_2}$ of 8.33. This value is below that for the lymphocytes themselves because of the presence of small quantities of other cells (connective tissue, etc.) by an amount that may be as much as 1.04 (as in subgroup C of stock Ak, reported in the first paper). Thus the $Q_G^{N_2}$ of malignant lymphocytes in the liver, estimated by extrapolation to 100 per cent infiltration, agrees very well with that of the lymph nodes of the same animals. This fact strongly supports the view that the high anaerobic glycolysis rate of the leukemic liver is in part due to the metabolic activity of the lymphocytes infiltrating it.

Second, the regression line intercepts the $Q_G^{N_2}$ axis (*i.e.*, at zero infiltration) at a value of 1.50. In other words, a liver from a leukemic mouse should have a $Q_G^{N_2}$ of 1.50 even if there are no malignant lymphocytes in it. That this is not merely a mathematical abstraction is shown by the finding in this series of one leukemic mouse (He 679), the liver of which proved on histological examination to be free of leukemic cells yet which had a $Q_G^{N_2}$ of 3.35. Apparently, then, the leukemic state of the animals confers upon the parenchymal cells of the liver the capacity to carry on active anaerobic glycolysis. This is a second reason for the observed high value of the anaerobic glycolysis rate of leukemic liver.

Possible differences between the anaerobic glycolysis rate of malignant lymphocytes in the liver and in the lymph nodes.—The problem of whether the metabolic activity of malignant cells is influenced by different types of normal cells surrounding them has received little attention. Crabtree (6) implanted Jensen rat sarcoma subcutaneously and intraperitoneally into rats and found that the $Q_G^{N_2}$ values of the resultant tumors were almost identical, although the Q_{O_2} and $Q_G^{O_2}$ were greater in the subcutaneous tumors. It would be unwise to assume, however, that the results of Crabtree's studies, in which the malignant cells were in contact only with connective tissues, are comparable to those of studies in which the malignant cells have actively metabolizing liver cells in their immediate environment.

A factor that might be expected to cause the

anaerobic glycolysis rate of lymphocytes in the liver to differ from those in the lymph nodes is the potential availability of glucose derivable from breakdown of the glycogen of the hepatic cells. It has been shown (10) that leukemic lymph nodes in the absence of glucose exhibit no anaerobic glycolysis, in other words, do not glycolyze their intracellular constituents. This fact makes them sensitive test objects for glycolyzable substances in their fluid environment.

Accordingly the anaerobic glycolysis rates of liver slices from 4 leukemic mice were determined in the presence of 0, 200, and 400 mgm. per cent glucose.[1] The results, given in Table IV, bring out the following points:

First, since in a glucose-free medium the average $Q_G^{N_2}$ of liver tissue was -0.02, the liver parenchymal cells liberate at most very small quantities of glucose into the environment of the malignant lymphocytes.

Second, the determinations of liver $Q_G^{N_2}$ were regularly made in 200 mgm. per cent glucose. Increasing the glucose concentration to 400 mgm. per cent did not increase (but slightly reduced) the $Q_G^{N_2}$ of leukemic liver. Accordingly, even if the parenchymal cells did give off glucose, the anaerobic glycolysis rate of the slices would not have been altered significantly.

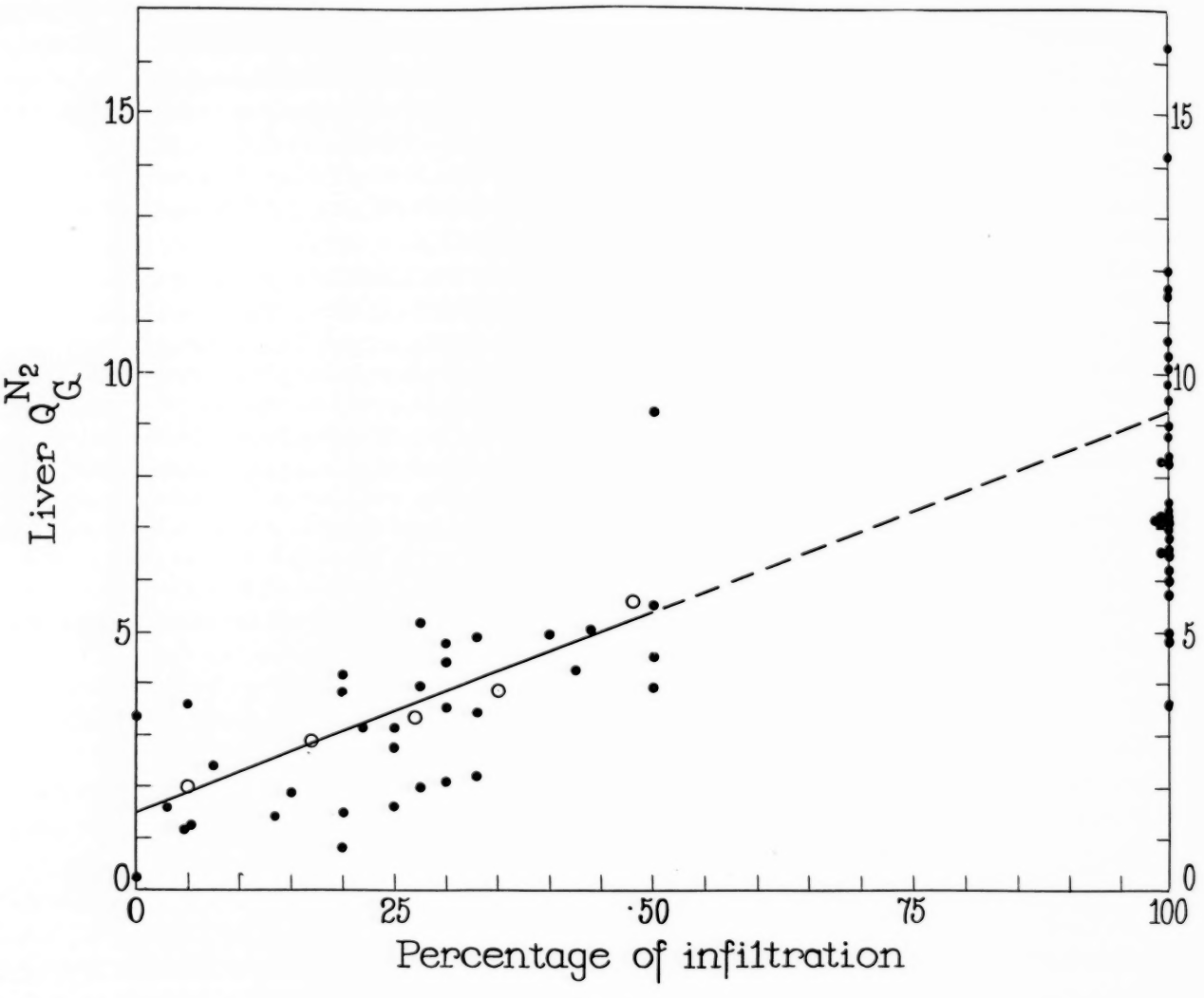

FIG. 1

TABLE IV: EFFECT OF GLUCOSE CONCENTRATION ON THE RATE OF ANAEROBIC GLYCOLYSIS OF LEUKEMIC LIVER

Mouse number	$Q_G^{N_2}$ of lymph nodes	Glucose concentration (mgm. per cent) 0	200	400
Akf113	4.65	— 1.31	4.92	5.39
Akh84	4.86	— 0.63	2.20	1.83
Akh118	14.23	1.57	3.14	3.03
Hb134	15.48	0.31	5.13	4.03
	Averages	— 0.02	3.85	3.57

[1] Cytological examination of the livers showed in three cases no abnormality of the parenchymal cells except for slight vacuolization. One showed considerable fatty degeneration; however, it was not unusual in its metabolic behavior.

We may conclude that the hepatic environment of the leukemic lymphocytes, at least in so far as glucose is concerned, should not cause their $Q_G^{N_2}$'s to differ from what they would have been in the lymph nodes. It is possible, however, that the liver cells might provide other substances, such as constituents of enzyme systems or intermediates, that might affect the glycolytic activity.

Turning now to data concerning the relation between the anaerobic glycolysis rates of malignant lymphocytes in the liver and in the lymph nodes, we may first consider the group of mice as a whole. As stated above, the $Q_G^{N_2}$ of these cells in the liver may be estimated by extrapolating the regression line (Fig. 1) to 100 per cent infiltration—which yields a $Q_G^{N_2}$ value of 9.23. The lymph nodes from the same animals have an average $Q_G^{N_2}$ of 8.33; that of the malignant cells themselves would be somewhat higher. The agreement is close enough to support the conclusion that the anaerobic glycolysis rate of the lymphocytes at these two sites does not differ significantly.

Among the individual cases there is considerable scatter, both in the liver $Q_G^{N_2}$ values around the regression line (Fig. 1), and in the lymph node $Q_G^{N_2}$'s around their mean. If the anaerobic glycolysis rate of the lymphocytes is the same in liver and lymph nodes, there should be a positive correlation between the deviation of liver $Q_G^{N_2}$ values from the regression line, and the deviation of lymph node $Q_G^{N_2}$ values from their mean. However, when plotted, these reveal no significant relation. Either there is no tendency for these to vary or the tendency is obscured by variation from other sources, especially in the glycolytic activity of the parenchymal cells. In view of good agreement between liver and lymph node in the group as a whole, the second of these alternatives seems preferable.

Enhanced glycolysis by the parenchymal cells of the liver.—It has previously been reported that in certain malignant or premalignant states the parenchymal cells of the liver develop the capacity to carry on anaerobic glycolysis at a rate much above that of normal liver. Büngeler (2) found that the livers of mice bearing certain transplantable tumors showed an increased anaerobic glycolysis rate when the tumors became necrotic; this also occurred in the livers of mice with spontaneous mammary carcinoma, the increase in $Q_G^{N_2}$ being proportional to the degree of tissue reaction about the tumor. In all cases the livers showed some histological changes but in none had the tumor metastasized to the liver. In rats fed *p*-dimethylaminoazobenzene the anaerobic glycolysis rate of the liver increased definitely before tumor cells were demonstrable in the liver (Nakatani, Nakano, and Ohara [13]; Burk, Behrens, and Sugiura [3]). In rats that had been given this compound there is evidence of degeneration and regeneration of liver cells, proliferation of bile ducts, and apparent increase of Kupffer cells. Although the increased rate of anaerobic glycolysis under conditions just mentioned may be due in part to the metabolic activity of white blood cells, proliferating histiocytes and endothelial cells, fibroblasts, or other cells in the liver, the extent of such changes is hardly likely to be adequate to explain the changes observed. Since there are no malignant cells in the liver tissue in the experiments just described, it seems most probable that the liver cells themselves are responsible for the rapid anaerobic glycolysis developing in these premalignant states.

Two lines of evidence suggest that a similar increase in the anaerobic glycolysis rate of liver parenchymal cells may be present in at least some of our leukemic animals. First, in one (He 679) of the two leukemic livers found on histological examination not to contain malignant lymphocytes there was nevertheless a high $Q_G^{N_2}$ value, 3.35; in the other case (Ha 21), however, it was only 0.26. Second, as mentioned in a previous section, the regression line representing the linear relation of liver $Q_G^{N_2}$ to percentage of infiltration intercepts the $Q_G^{N_2}$ axis (*i.e.* at zero infiltration) at a value of 1.50. There is considerable scatter of the points representing individual cases about the regression line, Accordingly, the results indicate that the leukemic state of the animal may or may not increase the anaerobic glycolysis rate of the liver parenchymal cells, depending on conditions hitherto unknown.

Concerning the mechanism of this effect nothing is known. However, it may be pointed out that there is continuous multiplication, dissemination, and destruction of malignant lymphocytes, as a consequence of which substances may be liberated that might affect the metabolism of liver cells. Such a situation would parallel in certain respects that described by Büngeler (2), in which increased liver anaerobic glycolysis was associated with necrosis of tumors located outside of the liver. Further, Albaum and Potter (1) have found that extracts of necrotic, but not of healthy, tumors inhibit the succinoxidase activity of liver homogenates.

The influence under discussion here is apparently only one manifestation of a widespread effect. The presence of a tumor in the body has been shown to influence a wide variety of biochemical processes in host tissues remote from the site of the tumor. The investigations in this field have been briefly reviewed by Burk and Winzler (5). It is not clear, however, that any of the changes reported bear any close relation to that in the anaerobic glycolysis of the liver.

SUMMARY

The oxygen consumption of liver tissue from mice with lymphoid leukemia is greater than that of normal liver tissue, its aerobic glycolysis rate is somewhat lower, and its anaerobic glycolysis rate is much higher.

The increase in anaerobic glycolysis rate is attributable to two factors: (a) the presence in the liver of malignant lymphocytes that are carrying on anaerobic glycolysis at a rate similar to that of the same cells in the lymph nodes; and (b) a considerable increase in the glycolytic activity of the parenchymal cells of the liver, which can be independent of the presence of leukemic cells in the organ and which appears to be due to the leukemic state of the animal.

The author wishes to thank Dr. Jacob Furth, in whose laboratory this work was done, for guidance in the pathologic aspects of the problem, and Dr. Dean Burk for the many helpful comments and suggestions that have been used in the preparation of this paper.

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Transplantation of Plant Tumors of Genetic Origin

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The occurrence of tumorous growths on hybrids between *Nicotiana langsdorffii* and *N. glauca* has been reported and the behavior of these growths described in considerable detail by Kostoff (1-3), Whitaker (6), Levine (4), and others. Their resemblance to certain types of animal and human teratomas has been pointed out by Kostoff and Levine. Kostoff made some unsuccessful attempts to transplant these tumors.

In 1937 tissue cultures were isolated from growths of this type (7) and were used in studies on control of differentiation in undifferentiated tissue masses (8, 5). These cultures are now (May 10, 1944) in the 144th passage *in vitro*. Later (1941) similar cultures were isolated from bacteria-free crown-gall tissue of sunflower having an entirely different, nongenetic origin (10). These have likewise been maintained *in vitro* and are now in the 76th passage.

The successful implantation of tissue of bacteria-free crown-gall cultures into sunflower and artichoke after long cultivation *in vitro*, the production of new tumors therewith, and the bearing of these grafts on the whole question of homology between plant tumors and animal neoplasms (10, 11) suggested the importance of reexamining the genetic tumors for similar properties. The work on bacteria-free crown-gall tumors also furnished valuable experience in the necessary technic. This paper presents the results of experiments on the transplantation from one host to another of tissue derived from a plant tumor of genetic origin.

MATERIALS AND METHODS

Attempts to graft small pieces of tumor tissue from *Nicotiana langsdorffii* × *N. glauca* hybrids directly into other hybrid plants are obviously doomed to failure,

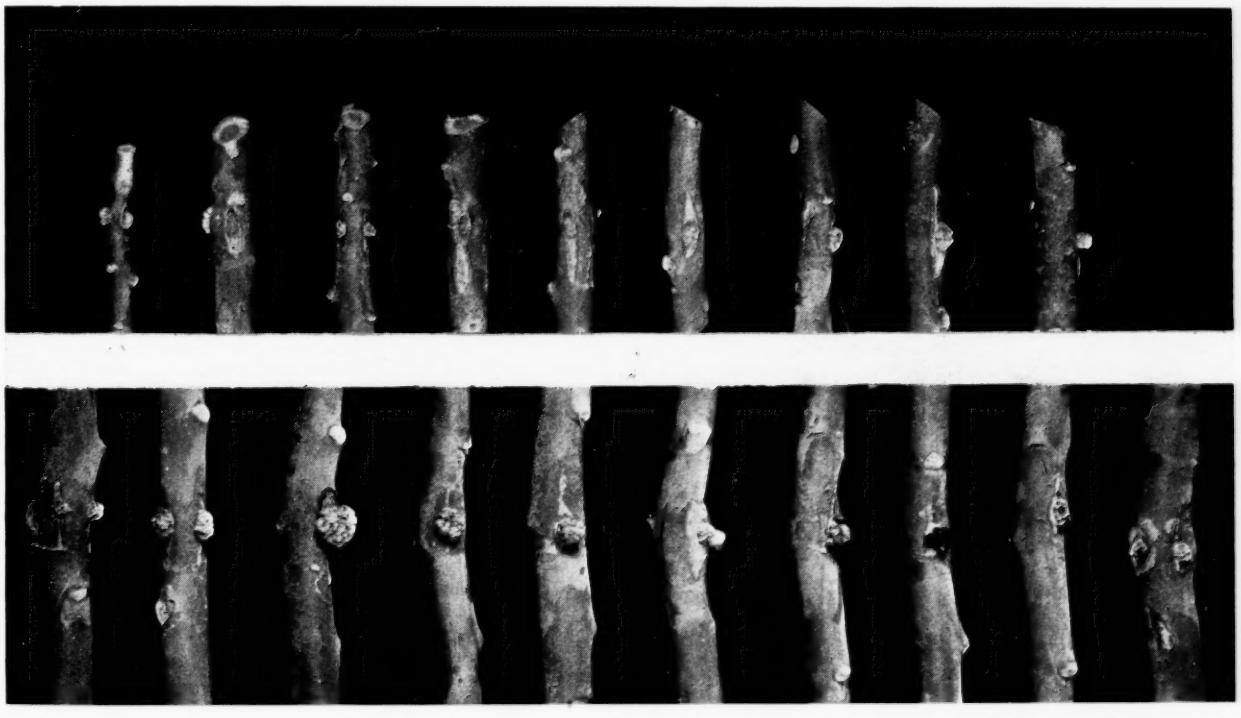

FIG. 1.—Bottom row, tumors obtained by grafting under the bark of *Nicotiana glauca* 10 fragments of sterile callus tissue from the hybrid *Nicotiana langsdorffii* × *N. glauca* and maintained for about 5 years *in vitro* before implantation. Eighteenth week after implantation. In first and second examples from left, and last one at right, tumors have emerged through *both* incisions. Mag. × 0.6.

Top row, similar series of 9 tumors. Tenth week after implantation. Mag. × 0.6.

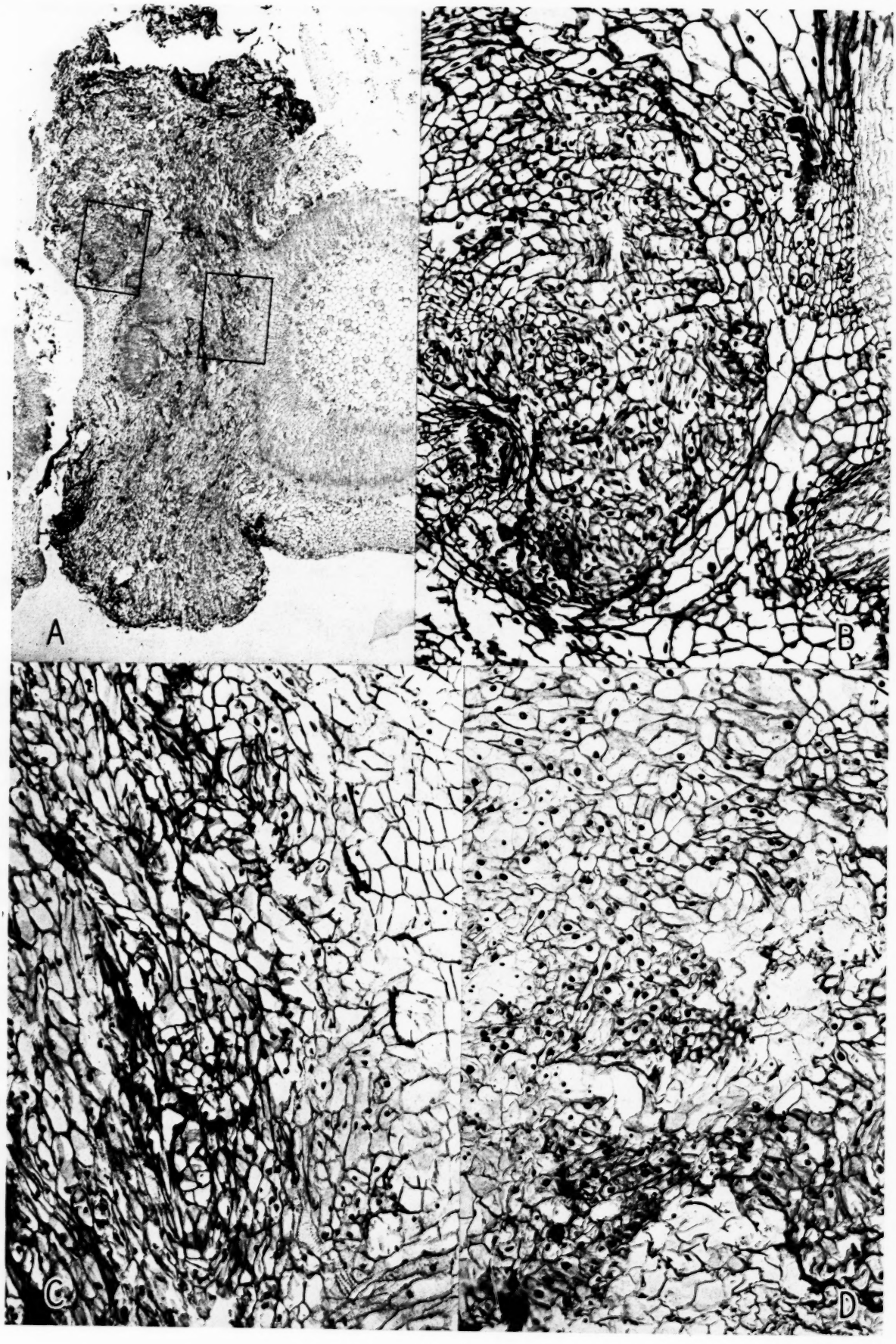

FIG. 2

since any wound to such a plant regularly results in a massive callus overgrowth that would automatically destroy anything but a fairly broad graft union. Grafts to non-tumefacient species of *Nicotiana* would avoid this mechanical difficulty but might, as Kostoff has emphasized, encounter physiological barriers or incompatibilities. Grafts attempted on *Lycopersicon esculentum, Nicotiana tabacum,* and *N. glutinosa* did, in fact, consistently fail. This physiological difficulty should, however, be minimal when grafts are made back upon either parent of the hybrid. Grafts to *Nicotiana langsdorffii* gave occasional possible "takes" but these were uncertain, because of the extensive callusing characteristic of all wounds on this species. Grafts to *Nicotiana glauca* were much more unequivocally successful and will be reported in detail.

For this purpose rapidly growing 5 year old tissue cultures were cut into thin slices, about 0.2 mm. thick and 2 to 3 mm. in diameter. Young stems of *Nicotiana glauca* were stripped of their leaves 3 to 5 cm. back of the growing point. In each, a pair of parallel incisions about 3 mm. apart and 7 to 8 mm. long were made with a sharp scalpel, the cuts being so placed as to meet at or a little below the cambium level. This formed a flap of cortex which, when the stem was bent toward the cut side, could be made to buckle outward, exposing the cambial region. A slice of tumor culture tissue was inserted in this incision and the stem allowed to return to its normal position, thus pulling the cortical flap tight. The incision was wrapped with "Sterilastic" rubber tape and allowed to heal. The bandages were removed 2 weeks after the operation.

EXPERIMENTAL RESULTS

In one series of 20 grafts set up February 2, 1943, there were, at the end of 14 days, 6 takes, 4 possible takes, and 10 negatives. At the end of 36 days the takes had increased to 8 (40 per cent), ranging up to 5 mm. in diameter; there were two new "possibles"; one previously recorded as possible was relegated to the negative class; and 8 of the negatives remained unchanged. Photographs of two series set up on February 25, 1943, and October 4, 1943, are shown in Fig. 1. The percentage of takes (40 per cent in the February 2nd series, 32 per cent in the February 25th series, and 54 per cent in the October 4th series) was excellent. The tumors formed were small in comparison with those produced on *Helianthus* by grafting bacteria-free tumor tissue cultures, but were essentially similar to these in general appearance.

Sections showed a structure similar to that observed in *Helianthus* tumor grafts (Fig. 2). In the example shown in transverse section (Fig. 2A) the implant had spread out both to right and left, producing tumors in *both* incisions, which were externally discrete but internally continuous (No. 2 from the left, bottom row, Fig. 1). A considerable mass of unaltered cortex, including vascular strands, was left at the center. Characteristic disoriented masses of cells occurred at the boundary between tumor and healthy cortex (Fig. 2B) and between tumor and host xylem (Fig. 2C). The rapidly growing outer part of the tumor was even more disorganized. The contrast between size of nuclei in rapidly growing and in degenerating portions of this mass is especially striking (Fig. 2C).

DISCUSSION

The spontaneous tumors that regularly arise at traumatized loci on plants of the hybrid, *Nicotiana langsdorffii* × *N. glauca,* were long ago recognized as malignant in the sense of regularly destroying plants upon which they appear (1). Levine (4) considered the degree of disorganization somewhat limited since he believed that he could recognize definite bud primordia in the superficial regions of all tumors *in situ*. In tissue cultures maintained on an agar substratum these bud primordia are no longer recognizable although they can be evoked by reducing the oxygen

DESCRIPTION OF FIGURE 2

FIG. 2.—Transverse sections of tumors obtained by implanting hybrid tumor tissue cultures under bark of *Nicotiana glauca.*

A. General picture. At right, host stem with normal pith, wood, and cortex; at left, a tumor (compare Nos. 1, 2, and 10 of bottom row, and Nos. 1, 2, and 3 of top row, Fig. 1). Note fairly wide region of normal epidermis and cortex (left, center) between the two tumors. Mag. × 14.5.

The two blocked areas are: Center, Fig. 2C; upper left, Fig. 2B.

B. Detail of tumor mass at region of contact between tumor and healthy host cortex. At right, host xylem (wood) with phloem bundle at upper right, flanked above and below with cortical parenchyma. The disorganized tumor mass occupies center and left hand portion of picture. A sharp, dark line of gummy material bounds the tumor mass, and at the bottom is some evidence of crushing of cortical parenchyma. Scalariform cells, characteristic of tumor tissue (compare White and Braun [10] Fig. 6; White [9] Fig. 67), evident at many points in tumor mass. Mag. × 112.

C. Detail of contact between tumor tissue (left) and host xylem (right). Line of original incision shown by dark, gummy masses at right. Much of tumor mass likewise shows gummy deposits on the cell walls. *Note again* scalariform cells in tumor tissue. Mag. × 112.

D. Detail of central portion of another younger tumor. Note complete lack of orientation in cells, and scattered areas containing very small, pycnotic nuclei, mostly in regions that show considerable breakdown of the tissue. Mag. × 112.

tension of the medium (8), by reducing the intensity of illumination (5), and probably by other means. The degree of disorganization is thus not definitely fixed. The experiments reported here have demonstrated that these tumors possess the additional property, commonly attributed to neoplasia, of producing new tumors of similar type upon grafting into healthy individuals of a related species (the parent species, *Nicotiana glauca*), which is not naturally subject to tumefaction and never produces spontaneous tumors. The writer considers the retention of the tumefacient property after 5 years *in vitro* and its expression in a non-tumefacient host as evidence of the fundamental character of this property, in this case a property of genetic origin.

SUMMARY

Tissues isolated from stems of the hybrid, *Nicotiana langsdorffii* × *N. glauca,* which normally produces tumorous overgrowths spontaneously, after being maintained as *in vitro* tissue cultures for 5 years, were grafted into healthy plants of *Nicotiana glauca.* Here they produced typical tumors. They thus appear to possess the property of propagating their tumorous nature, in this case of genetic origin, indefinitely. Possible implications of this fact are discussed briefly.

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Abstracts

Experimental Research, Animal Tumors

Die Auslösung einer Riesenform bei Seeigelkeimen durch das krebserregende Benzpyren. [Formation of Giant Forms of Sea Urchin Embryos under the Influence of the Carcinogen Benzpyrene.] DRUCKREY, H. [Univ. Berlin, Berlin, Germany] *Naturwissenschaften,* **30**:734-735. 1942.

Eggs of the sea urchin *Strongylocentrotus lividus* were suspended for 1 hour in sea water saturated with benzpyrene. They were then fertilized, and their development in normal sea water was observed for the first 7 days after fertilization. At the pluteus stage giant forms appeared. None appeared among several hundred controls, which were either not treated or treated with noncarcinogenic substances.—Z. D.

Some Factors that Influence the Growth of Neoplastic Cells. KLINE, B. E., and RUSCH, H. P. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research,* **4**:762-767. 1944.

Methylcholanthrene was applied to the skin of mice for a period just short of that necessary for the formation of visible tumors. The skin was then treated with naphthoquinone, croton oil, croton oil resin, or sodium sulfide, or was subjected to frequent incisions. In every case many tumors developed subsequently, except after sodium sulfide, which was ineffective.

Frequent incisions made through the abdominal wall of rats with primary hepatomas resulted in nests of proliferating hepatoma cells in the regions of the wound. These neoplasms regressed during the later stages of the healing process. It is suggested that such transplanted cancer cells found a favorable environment for growth in the region of the healing wounds, and that the defense mechanism of tissues that inhibit such growth normally is decreased in areas where reparative processes are active.

These results are correlated with the suggestion that tumor formation may be divided into three phases: (a) period of induction, during which the neoplastic cell is formed; (b) critical or reversible period, in which the growth of the neoplastic cell is in delicate balance and depends upon the local tissue environment; and (c) the final period of progression, during which growth is relatively unchecked.—Authors' abstract.

Influence of Bromobenzene on the Induction of Skin Tumors by 3,4-Benzpyrene. CRABTREE, H. G. [Imperial Cancer Research Fund, Mill Hill, England] *Cancer Research,* **4**:688-693. 1944.

The carcinogenic action of 3,4-benzpyrene on mouse skin is inhibited and sometimes prevented by local applications of bromobenzene to the skin 4 times weekly. In a precancerous area of skin, bromobenzene greatly delays and often prevents the emergence of visible tumors. The influence of bromobenzene is local, and evidence is given that it is due to intermittent interference with sulphur metabolism. Glutathione and ascorbic acid levels in the skin are lowered quickly after bromobenzene treatment, but recover to normal values after a few hours. All the chemical and biological evidence supports the view that bromobenzene is detoxicated by mercapturate formation in the skin before being excreted in the urine.

The possible relation of sulphur metabolism to carcinogenesis is discussed.—Author's abstract.

Mast Cells in Experimental Skin Carcinogenesis. CRAMER, W., and SIMPSON, W. L. [Barnard Free Skin and Cancer Hosp., St. Louis, Mo.] *Cancer Research,* **4**:601-615. 1944.

A pronounced increase in the number of tissue mast cells accompanies the carcinogenic process induced in mouse skin by minimal total doses of methylcholanthrene. The mast cell reaction is evident long before a carcinoma appears. It occurs in association with, and seems to be conditioned by, the development and degree of nonneoplastic epidermal hyperplasia. Mast cells disappear from the cancer itself probably by being destroyed, although contiguous areas of dermis beneath precancerous hyperplastic epithelium often show the most striking accumulations of these cells.

Histochemical studies reveal that the mast cells in areas of considerable hyperplasia are altered from the normal prototype. Two kinds of chromotrope substance were found, one soluble, one insoluble in watery fixatives. Progressive changes in the kind and amount of these substances, in the total load of stainable granules, and in the size of the cells suggest that a continuous process of histogenous development and maturation of these cells occurs in such areas. From the superficial dermis to the deeper parts, the mast cells fall into general classes of "agranular," "ametachromatic," and "metachromatic" types. Further evidence of structural change is the fact that "agranular" and "ametachromatic" cells exhibit strong golden-brown fluorescence in ultraviolet light. Normal mast cells fluoresce weakly or not at all. The possible significance of the mast cell reaction in the light of recent work on heparin, hyaluronic acid, and other polysulfuric acid esters of high molecular polysaccharides is discussed.

The regular occurrence of a mast cell reaction beneath hyperplastic epidermis, absence of these cells from carcinomas, and their presence to an abnormal degree in the skin of mice resistant to limited methylcholanthrene treatment suggest that the response is associated with a defensive process against the development of skin cancer.—Authors' abstract.

Ribonucleic Acid and Heterochromatin in Epidermal Carcinogenesis. BIESELE, J. J. [Univ. of Pennsylvania, Philadelphia, Pa.] *Cancer Research,* **4**:737-750. 1944.

In mouse epidermis painted with methylcholanthrene in benzene, the ribonuclease-pyronin technic indicated a

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notable increase in cytoplasmic ribonucleic acid concentration by one-half day after treatment. Ribonucleic acid was at a maximum from the third to the tenth day and thereafter dropped to an intermediate value by the 57th day. It was high again in the one cancer studied and remained at normal levels in controls treated with benzene alone.

Nuclei bearing multiples of the normal number of heterochromatic segments were in evidence from the second day of methylcholanthrene treatment on through carcinogenesis and were predominant in the cancers, as a study of acetocarmine preparations revealed. Such nuclei, which also contained increased numbers of plasmosomes and were relatively large, were closely paralleled in frequency by metaphases containing enlarged chromosomes. It is doubtful that there is any increase in number or size of heterochromatic segments in either hyperplasia or carcinoma induced by methylcholanthrene that is not explicable on the basis of multiple-stranded chromosomes and polyploidy.—Author's abstract.

Alkaline Phosphatase in Mouse Skin under Methylcholanthrene Treatment. Biesele, J. J., and Biesele, M. M. [Univ. of Pennsylvania, Philadelphia, Pa.) *Cancer Research*, **4**:751-755. 1944.

Alkaline phosphatase was studied histochemically in mouse skin painted with methylcholanthrene in benzene. By the second and third days after the beginning of treatment, considerable phosphatase activity was evident in the nuclei of the epidermal basal cells and in the reticular layer of the dermis. As epidermal hyperplasia progressed and the hair follicles were destroyed, the enzyme became less concentrated in the epidermis and the reticular layer, but it was still abundant in the skin on the edge of the region of greatest histological reaction to the carcinogen, much like the collar of positive cells about a healing skin wound. The enzyme concentration in the basal cells was in direct proportion to the closeness of positive dermal elements, such as capillaries. In the carcinomas and papillomas studied the alkaline phosphatase reaction was very intense both in the stroma and in the epidermal cells lying close to the stroma, but the phosphatase was practically absent from cells far removed.—Authors' abstract.

Studies on Plant Tumors. Part II. Carbohydrate Metabolism of Normal and Tumor Tissues of the Beet Root. Neish, A. C., and Hibbert, H. **Part III. Nitrogen Metabolism of Normal and Tumor Tissues of the Beet Root.** Neish, A. C., and Hibbert, H. **Part IV. Oxidases in Normal and Tumor Beet Root Tissue.** Levi, I., Michaelis, M., and Hibbert, H. [McGill Univ., Montreal, Canada] *Arch. Biochem.*, **3**:141-157; 159-166; 167-174. 1943.

—H. J. C.

"d-Peptidase" im menschlichen Organismus. Ein Beitrag zur "Köglschen Geschwulsttheorie" und zur "stereochemischen Analyse von Proteinen." Zur Kenntnis der Peptidasen. III. Mitteilung. [*d*-Peptidase in Man. Contribution to Kögl's Tumor Theory and to the Stereochemical Analysis of Proteins. Studies on Peptidases. III.] Bamann, E., and Schimcke, O. [Univ. Tübingen, Tübingen, Germany] *Biochem. Ztschrft.*, **310**:131-151. 1941.

A comparison was made of the activities of *d*- and *l*-peptidases in water extracts from fresh human organs, 3 mammary carcinomas, and a liver metastasis of one of them. No significant difference between normal and tumor cells was found. The fact is reported without any experimental details, that when a mixture of *d*- and *l*-peptidases acts on a mixture of *d*- and *l*-peptides only the latter is split. The possible importance of this phenomenon from the point of view of Kögl's tumor theory is discussed at length.—Z. D.

Zur Kenntnis tierischer Peptidasen. XII. Mitteilung. Über Amino-peptidasen des Mäuse-Ascites-carcinoms. [Animal Peptidases. XII. Amino-peptidases of Mouse Ascites Tumor.] Maschmann, E. [Forschungsinst. f. Chemother., Frankfurt a. M., Germany] *Biochem. Ztschrft.*, **311**:374-384. 1942.

The *l*- and *d*-amino di- and tripeptidases of the ascitic fluid and of the cells suspended in it (tumor and exudate cells) were compared with normal cells (previously investigated) as to their activity and sensitivity to heavy metals and to substances forming complexes. The cell enzymes were extracted with 10 parts of water from the cell powder obtained by drying with acetone. Tumor cells growing on the peritoneum also were examined. No significant differences between tumor and normal cells were found.—Z. D.

Zur Kenntnis tierischer Peptidasen. XV. Mitteilung. Über l- und d-Peptidasen von Organen und des Blutserums normaler, sarkom-resistenter, sarkomatöser und spontan geheilter Ratten und des Jensen-Sarkoms. [Animal Peptidases. XV. *l*-and *d*-Peptidases in Organs and Blood Serum of Normal, Sarcoma-Resistant, Sarcoma-Bearing, and Spontaneously Recovered Rats, and in the Jensen Sarcoma.] Maschmann, E. [Forschungsinst. f. Chemother., Frankfurt a. M., Germany] *Biochem. Ztschrft.*, **313**:156-169. 1942.

The peptidases of tissue cells were examined as to their activity and sensitivity to heavy metals and complex-forming inhibitors in glycerol extracts from the acetone-dried tissue. One part of the desiccate was extracted with 2 parts of glycerol for 2 days at room temperature. No significant difference with respect to "natural" and "unnatural" peptidases was found between extracts from the various tissues tested, whereas the blood serum of tumor rats contained more *d*-peptidase than did the serum of normal rats.—Z. D.

Zur Kenntnis tierischer Peptidasen. XVII. Mitteilung: Ueber die Bindung "natuerlicher" und "unnatuerlicher" Peptidasen in Organ- und Tumorzellen. [Animal peptidases. XVII. The Linkage of "Natural" and "Unnatural" Peptidases in Tissue and Tumor Cells.] Maschmann, E. [Forschungsinst. f. Chemother., Frankfurt a. M., Germany] *Biochem. Ztschr.*, **315**: 1-25. 1943.

This posthumous paper contains a large number of experiments on the behavior towards extraction and drying procedures, of "natural" and "unnatural" dipeptidases and "natural" aminopolypeptidases of the liver and kidney tissue of rabbits, guinea pigs, and rats, as well as of mouse carcinoma and sarcoma, and rat sarcoma tissue. The substrates employed were leucyl-glycine, alanyl-glycine, glycyl-alanine, glycyl-leucine, glycyl-glycine, leucyl-glycyl-glycine, alanyl-glycyl-glycine, glycyl-glycyl-

glycine (all containing the "natural" forms) and the "unnatural" *d*-leucyl-glycine, glycyl-*d*-leucine, and glycyl-*d*-alanine.

The bulk of the liver, kidney, and tumor peptidases appears to be present in the tissues either in dissolved or in readily soluble form, *i.e.*, as *lyo-enzymes* in Willstätter's terminology, since they are extracted from the dried tissue powder by treatment with water for 10 min. at 0°C. Only a minor fraction of these enzymes is present in the form of insoluble *desmo-enzymes* or *endo-enzymes*. There appear to be small but significant differences in the solubility behavior of liver and tumor peptidases on the one hand, and kidney enzymes on the other. The ratio of lyo-peptidases to desmo-peptidases is subject to certain variations from enzyme to enzyme, species to species, and individual to individual. However, the ratio is invariably strongly in favor of the soluble forms.

Drying of the tissues with acetone, which is a rapid process, is always accompanied by more or less far-reaching impairment (denaturation) of the peptidases examined. Upon drying the tissue from the frozen state over P_2O_5 in high-vacuum, which is a relatively slow method, no appreciable damage to these enzymes was observed, the activity being equal to that of glycerol or water extracts of the fresh materials.—K. G. S.

The Ascorbic Acid Content of the Liver in Pregnant Mice. Kennaway, E. L., and Kennaway, N. M. [Royal Cancer Hosp. (Free), London, England] *Cancer Research,* **4**:704-706. 1944.

The concentration of ascorbic acid in the liver has been compared in pregnant and nonpregnant mice, and in the pregnant condition an increase was found that was significant in 3, and probably significant in 3 more, of the 7 strains examined. No other sexual conditions have been found in which such an increase occurs. Glutathione does not behave in this way. Some data are given on the increase in weight of the liver in pregnancy.—Authors' abstract.

Metabolic Studies in Mouse Leukemia. II. Metabolism of Livers of Mice with Lymphoid Leukemia. Hall, V. E. [Cornell Univ. Med. Coll., New York, N. Y., and Stanford Univ., Stanford Univ., Calif.] *Cancer Research,* **4**:785-790. 1944.

The oxygen consumption of liver tissue from mice with lymphoid leukemia was greater than that of normal liver tissue; the rate of aerobic glycolysis, somewhat lower, and of anaerobic glycolysis, much higher.

It is concluded that the increase in the rate of anaerobic glycolysis is attributable to two factors: (1) the presence in the liver of malignant lymphocytes that are carrying on anaerobic glycolysis at a rate similar to that of the same cells in the lymph nodes; and (2) a considerable increase in the glycolytic activity of the parenchymal cells of the liver, which can be independent of the presence of leukemic cells in the organ and which appears to be due to the leukemic state of the animal.—Author's abstract.

Changes in the Adrenal Glands of Rats Following Exposure to Lowered Oxygen Tension. Dalton, A. J., Mitchell, E. R., Jones, B. F., and Peters, V. B. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.,* **4**:527-536. 1944.

The present study deals with the changes occurring in the adrenal glands of rats subjected to lowered oxygen tension in single (4 hours) and repeated exposures of short duration (4 hours, 6 days a week). Immediately after a single exposure, the zona fasciculata usually contained less lipid than did the same zone in normal glands and resulted in the appearance of lipid droplets in the "lipid free zone" of the outer fasciculata. Twenty hours later all adrenals contained less lipid than normally, and the "lipid free zone" became unidentifiable as a result of the accumulation of numerous lipid droplets within it.

Repeated exposure to lowered oxygen tension caused adrenal hypertrophy, which reached a maximum at 6 weeks, and with continued exposure a gradual return toward the original size occurred. Also, animals exposed for more than 6 weeks possessed adrenal glands that contained approximately normal amounts of lipid, which was distributed in a normal pattern. The authors suggest that adaptation to conditions of lowered oxygen tension may result from discontinuous exposure after 6 weeks and discuss the significance of the changes in the lipid free zone in relation to the life history and functional activity of the adrenal cortical cells.—D. S.

Prothrombin Activity in Rats with Hepatic and Other Tumors. Field, J. B., Baumann, C. A., and Link, K. P. [Univ. of Wisconsin, Madison, Wis.] *Cancer Research,* **4**:768-771. 1944.

The presence in the rat of spontaneous mammary tumors, of induced skin tumors, or of inoculated Flexner-Jobling tumors does not cause a prolongation of the normal prothrombin time (12.5% plasma). On the other hand the presence of primary hepatic tumors due to *p*-dimethylaminoazobenzene may cause a mild hypoprothrombinemia. A standard dose (2.5 mgm.) of 3,3′-methylenebis(4-hydroxycoumarin) usually causes a more severe hypoprothrombinemia in rats with primary hepatic tumors than in normal rats or in rats bearing tumors in other parts of the body. The extent and duration of the hypoprothrombinemia is probably influenced by the amount of normal hepatic tissue present. While vitamin K protects normal rats against the hypoprothrombinemic action of a single dose of 3,3′-methylenebis(4-hydroxycoumarin), in rats with hepatic tumors this protective action is either lessened or abolished.—Authors' abstract.

The Dependence of the Genesis of Induced Skin Tumors on the Caloric Intake During Different Stages of Carcinogenesis. Tannenbaum, A. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research,* **4**:673-677. 1944.

Calorie-restricted diets inhibit the formation of various types of tumors in mice. Previous work suggested that the inhibitory effect occurs during the period in which tumors appear, rather than in the period of carcinogenic stimulation. The present experiment was designed to test this view. Four groups of 50 mice each were given equal applications of 3,4-benzpyrene to the skin; treatment was terminated before any tumors appeared. The groups differed in that the first received a calorie-restricted diet during painting, the second after painting, the third both during and after painting; the fourth received the *ad libitum* diet throughout. The percentages of skin tumors formed in these groups were 55, 34, 24, and 65 respectively.

The results suggest that carcinogenesis can be divided into 2 distinct phases: (1) a stage of preparation or initiation in which the normal cells become prepared or biased toward forming a tumor, and (2) a stage of development or formation that eventuates in a perceptible tumor. Furthermore, it was shown that (a) the initial fundamental changes due to the application of a carcinogen occur regardless of whether the mice are on a full or calorie-restricted diet, and (b) a full diet promotes the development of tumors from these initial changes, while a calorie-restricted diet inhibits such development.—Author's abstract.

The Importance of Differential Consideration of the Stages of Carcinogenesis in the Evaluation of Cocarcinogenic and Anticarcinogenic Effects. TANNENBAUM, A. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research,* **4**:678-682. 1944.

This communication is not a report of new experimental results. Pertinent reports in the literature are utilized in an attempt to clarify and extend the present concepts of the stages of carcinogenesis—initiation (pre-neoplastic) and development (neoplastic). Particular emphasis is placed on cocarcinogenic and anticarcinogenic effects of various agents and procedures, and an attempt is made to show that cocarcinogenic and anticarcinogenic actions may be, and generally are, effective during only one stage or the other (pre-neoplastic or neoplastic) of carcinogenesis.

As examples of the above, such procedures as wound healing, application of croton resin, and caloric restriction can affect the neoplastic stage, but have little or no effect on the pre-neoplastic stage. On the other hand, treatment with certain solvents and other procedures can have a definite effect during the pre-neoplastic stage, yet may be without significant effect during the neoplastic stage. It is possible that a particular agent or procedure may have one effect, cocarcinogenic, anticarcinogenic, or none, on the development of the pre-neoplastic stage, and another effect, cocarcinogenic, anticarcinogenic, or none, on the outcome of the neoplastic stage. The author stresses the desirability of testing, when feasible, the effect of a particular agent or procedure (solvent, chemical, hormone, inflammation, trauma, dietary change) during each stage of carcinogenesis as well as during the whole experimental period. Also discussed is the likelihood that such practice would increase our knowledge of the mechanism of carcinogenesis and its clinical implications.—Author's abstract.

The Dependence of the Genesis of Induced Skin Tumors on the Fat Content of the Diet During Different Stages of Carcinogenesis. TANNENBAUM, A. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research,* **4**:683-687. 1944.

A high-fat diet facilitates the formation of skin tumors. In the experiments reported, applications of 3,4-benzpyrene were made to the skin of mice for a limited period, being discontinued before any of the mice developed tumors. A group of mice that were fed a high-fat ration only during the period of carcinogen application developed no more tumors than did a control group on a low-fat ration. On the other hand, a group of mice receiving the high-fat ration in the period subsequent to application of carcinogen developed as many tumors as did a group that received the high-fat diet throughout the experiment. It was assumed that the period of application of carcinogen roughly corresponds to the initiatory stage of carcinogenesis, and that the period in which tumors appeared corresponds to the developmental stage. On the basis of this assumption, it was concluded that dietary fat has little or no effect on the initiatory stage, but that it has a significant facilitating effect on the developmental stage. This effect of ingested fat is differentiated from the effect of fat applied intentionally or by chance to the skin.—Author's abstract.

The Effect of Certain Lipids on the Carcinogenicity of *p*-Dimethylaminoazobenzene. MILLER, J. A., KLINE, B. E., RUSCH, H. P., and BAUMANN, C. A. [Coll. of Agric., Univ. of Wisconsin, Madison, Wis.] *Cancer Research,* **4**:756-761. 1944.

Fifteen groups of 15 rats each were fed various lipids in synthetic diets containing 0.06% *p*-dimethylaminoazobenzene for 4 months followed by dye-free diets for 2 more months. The strong anticarcinogenic effect of 5% of hydrogenated coconut oil was confirmed by the occurrence at 6 months, of 8% or less of hepatic tumors. When the hydrogenated coconut oil was replaced by corn oil, the tumor incidence increased to 73%. The removal of antioxidants from either oil did not affect these tumor incidences, and the addition of α-tocopherol to hydrogenated coconut oil likewise had no effect. When mixtures of the two oils were fed, the response tended to be characteristic of the major component of the mixture, though a greater effect was produced by a small amount of corn oil than of hydrogenated coconut oil.

The formation of hepatic tumors by rats kept on the diets studied did not depend upon the development or prevention of the syndrome characteristic of a deficiency of essential fatty acids. Relatively slight protection against hepatoma formation was obtained with diets containing 2½% trilaurin, the equivalent of the lauric acid contained in 5% hydrogenated coconut oil. Similar results were obtained with raw coconut oil. A tumor incidence of 69% was obtained with a diet free of added fat, thus demonstrating that dietary fat is not indispensable for the action of the dye. High tumor incidences were observed following both corn oil and hydrogenated coconut oil fed in diets containing crude casein and rice bran concentrate. A very low tumor incidence still occurred in rats given a diet containing hydrogenated coconut oil and 0.12% *p*-dimethylaminoazobenzene. No tumors were found in rats fed a corn oil diet with only 0.03% of the azo dye. It is suggested that the partition of the dye between the portal and lymphatic systems (Frazer) may be affected by the nature of the fat fed, with subsequent differences in metabolic breakdown.—Authors' abstract.

Structural Particularities of Antifibromatogenic Steroids: Experiments with Δ^4-Androstene-3,17-dione and Cholestenone. IGLESIAS, R., and LIPSCHÜTZ, A. [Nat. Health Service of Rep. of Chile, Santiago, Chile] *Proc. Soc. Exper. Biol. & Med.,* **55**:41-43. 1944.

The object of the experiment was to determine whether

Δ^4-3-ketosteroids that have little or no progestational activity are antifibromatogenic. Tablets of androstenedione or of cholestenone were implanted in castrated female guinea pigs simultaneously with estrogenic tablets. The latter when present alone induce abdominal fibroids in most animals in the course of 3 months.

The androstenedione was mixed with 20% cholesterol; 1 to 2 tablets of 25 to 30 mgm. each were implanted subcutaneously. Three to four tablets of pure cholestenone were implanted similarly. Autopsy was done 90 to 95 days after tablet implantation.

Quantities of androstenedione up to 40 times greater than the antifibromatogenic threshold of progesterone were not sufficient to prevent abdominal fibroids induced by α-estradiol. These quantities were also many times greater than the antifibromatogenic amounts of testosterone. The masculinizing action on the guinea pig clitoris was as great as with testosterone.

Amounts of cholestenone 10 times those of progesterone showed no antifibromatogenic activity.—M. B.

Differential Behaviour of the Liver Towards Natural and Artificial Estrogens. Lipschütz, A., Quintana, U., and Bruzzone, S. [Nat. Health Service of Rep. of Chile, Santiago, Chile] *Proc. Soc. Exper. Biol. & Med.*, **55**: 43-45. 1944.

Pellets of stilbestrol or of hexestrol were implanted subcutaneously, intrasplenically, or intrahepatically in 152 castrated female guinea pigs. Autopsy was performed 70 to 100 days later, and the fibrous tumoral reaction was classified in units previously employed by the authors.

The synthetic estrogens, stilbestrol and hexestrol, were more resistant to hepatic inactivation than were the natural ones. Abdominal fibroids could not be induced with intrasplenic pellets of natural estrogens, free or esterified; they were induced with the synthetic estrogens, although the incidence of tumors of a certain size was greatly diminished when compared with that resulting from subcutaneously implanted pellets. Toxic actions characteristic of prolonged treatment with estrogens were present also after intrasplenic implantation of pellets of the artificial estrogens.—M. B.

Comparative Fibromatogenic Action of Ovarian and Urinary Estrogens. Mello, R. F. [Nat. Health Service of Rep. of Chile, Santiago, Chile] *Proc. Soc. Exper. Biol. & Med.*, **55**:149-151. 1944.

Castrate female guinea pigs were given subcutaneous implants of pellets of the following estrogens: α-estradiol, estrone, estriol, equilenin, α-dihydroequilenin, β-dihydroequilenin. The pellets weighed from 3.5 mgm. for estradiol and estrone to 43 mgm. for the others. The ability of these estrogens to produce abdominal fibroids decreased among them in the order in which they are listed above. Ninety-one animals were used.—M. B.

The Urinary Excretion of Estrogens, 17-Ketosteroids, Creatine, and Creatinine in High and Low Mammary Tumor Strains of Mice. Karnofsky, D. A., Nathanson, I. T., and Aub, J. C. [Harvard Univ., and Massachusetts General Hosp., Boston, Mass.] *Cancer Research*, **4**: 772-778. 1944.

Metabolic differences between high and low tumor strains of mice and between litters of high and low tumor strain mice foster-nursed by the reciprocal mother are reviewed.

Comparative observations were made on C57 (low tumor strain) virgin and C3H (high mammary tumor strain) virgin and once-pregnant female mice. The C3H required more food than the C57 mice to maintain body weight. Both strains excreted approximately 0.5 mgm. creatinine per 20 gm. mouse per day.

The males and females of both strains excreted relatively large quantities of creatine in their urine. The creatine-creatinine ratios in the C57 and C3H females were similar until the tenth to 12th months of age, when the creatine output rose in the C57 and fell in the C3H strain mice. The C57 male mice consistently excreted more creatine than the C3H males.

Each mouse excreted in its urine an average of 1.2 to 3.3 international units of estrogens a month. The C57 mice appeared to excrete on the average slightly more estrogenic material (30%) than the C3H mice, but the difference is not considered significant. Both strains excreted 0.46 to 1.93 mgm. of a 17-ketosteroid-like substance per mouse per month with no appreciable strain differences.

Therefore, judged from urinary excretion rates there is as yet no evidence that high mammary tumor strain mice form or metabolize estrogens or 17-ketosteroid-like material in any significantly different fashion from a low tumor strain. Estrogens are to be regarded as an essential but not a specifically carcinogenic factor in the development of spontaneous mammary tumors in mice.—Authors' summary.

Effect of Long-Continued Administration of an Estrogen on the Sex Organs of Mice Which Have Passed the Reproductive Period. Crossen, R. J., and Loeb, L. [Washington Univ. Sch. of Med., St. Louis, Mo.] *Arch. Path.*, **37**:202-212. 1944.

Various kinds of growth processes are described in the sex organs of older female mice that have passed the breeding period and have been subjected to long-continued treatment with an estrogen in addition to the earlier action of the endogenous ovarian hormones. These proliferative changes are classified into (a) intensified normal growth processes, (b) abnormal growth processes, (c) precancerous and (d) cancerous changes.

Chronic mechanical stimuli, as well as long-continued inflammatory changes due to infection, may help to intensify some of the growth processes caused by hormones. There is no indication that acute regenerative processes have such an effect.

In the course of these carcinogenic stimulations conditions may develop that affect the stimulated tissues in such a way that their growth response is inhibited.

The various tissues of the secondary sex organs differ in their ability to respond to stimuli with proliferative changes that ultimately may lead to cancer. In the same individual, organ and tissue differences may be involved that are determined only indirectly by genetic factors; there exist also differences in the responsiveness of corresponding organs and tissues in different individuals and species, which are determined by genetic factors more directly and in a manner that is specific for these individuals and species.

It has been shown that within the same inbred strain or individual there probably exists, in addition to these differences in the mode of reaction of different tissues and organs to stimuli, a parallelism in intensity of the reactions of the various tissues and organs. This parallelism depends on the intensity of the hormonal stimuli, which differs in different animals, but which affects all the tissues in a given mouse with the same relative strength.

These experiments indicate that the increase in the incidence of cancer with advancing age of animals belonging to inbred strains is largely due to the accumulation of chronic stimulations of growth. At far as growth processes and cancerous processes are concerned, the tissues of older and those of younger organisms seem to differ only quantitatively in their reactions; the modes of their reactions seem to be similar.

It has, furthermore, been shown that the addition of an exogenous estrogen to the previously active endogenous ones may intensify certain growth processes initiated by the latter or may initiate other growth processes.—Authors' summary.

Influence of Breeding on Induction of Mammary Cancer with Methylcholanthrene in Strain Dba Female Mice. Kirschbaum, A., Lawrason, F. D., Kaplan, H. S., and Bittner, J. J. [Univ. of Minnesota Med. Sch., Minneapolis, Minn.] *Proc. Soc. Exper. Biol. & Med.*, **55**:141-142. 1944.

Twenty-three out of 26 control breeding females of strain dba (subline 12) developed spontaneous mammary cancer at an average age of 370 days (range: 300 to 460 days).

Two groups of female progeny, 6 to 8 weeks old, from these breeders, were put on similar diets and given 2 cutaneous applications weekly of a 0.5% solution of methylcholanthrene in benzene. The 27 females in group I were bred, each mouse having one or more litters. Thirty-one females in group II were maintained as virgins. Forty-eight male mice were similarly treated with methylcholanthrene.

All animals in group I developed mammary cancer after an average treatment period of 105 days. In group II only 4 of 31 mice produced mammary cancer; the average induction period was 190 days. Sixty-five percent of the males and virgin females developed leukemia; none of the untreated control breeders developed leukemia spontaneously.—M. B.

Genetic and Certain Non-Genetic Factors with Reference to Leukemia in the F Strain of Mice. Kirschbaum, A. [Univ. of Minnesota Med. Sch., Minneapolis, Minn.] *Proc. Soc. Exper. Biol. & Med.*, **55**:147-149. 1944.

Mice of the F strain, which have a spontaneous leukemia incidence of 53%, were crossed with animals of strains A, CBA, and C57, in which the leukemia incidence is less than 1%. In F_1 hybrids and backcrosses to the high leukemia stock, the incidence of leukemia was about the same as in the pure F stock; in the backcross to the low leukemia stock the incidence of leukemia was decreased. The retarded appearance of leukemia in the hybrid animals may be significant and might be correlated with the degree of inheritance from strain F or with the increased life expectancy in hybrids.

Gonadectomy did not alter the incidence of spontaneous leukemia in either sex; and there was no evidence for the existence of a leukemia "milk influence."—M. B.

The Genetics and Linkage Relationship of the Inherited Susceptibility to Mammary Cancer in Mice. Bittner, J. J. [Univ. of Minnesota Med. Sch., Minneapolis, Minn.] *Cancer Research*, **4**:779-784. 1944.

Reciprocal F_1 hybrids produced by mating mice of one low cancer (C57 black) and one high cancer (A) strain and nursed by females of the cancerous stock gave, in breeding females, approximately the same incidence of spontaneous mammary cancer. No evidence was secured to suggest any intrauterine influence for the development of mammary cancer in mice. The incidence in the total number of F_1 hybrids nursed by females of the A stock did not differ significantly from the incidence found in mice of the cancerous A stock.

Although the pooled data obtained in all the various types of hybrid generations could be accounted for on the genetic theory that the inherited susceptibility for mammary cancer in this cross was transmitted as a single dominant factor, it became evident on analysis of the incidence of cancer in the several subgroups that such a simple interpretation is inadequate and that other factors are probably involved. Detailed analysis showed: (1) That the incidence of mammary carcinoma in the F_2 hybrids with brown coat color was significantly higher than in their litter mates with black or albino coats. (2) That not all brown mice became cancerous, nor was the incidence in brown mice as high as in mice of the high cancerous A stock. (3) The progeny of brown mothers had a higher incidence than did the progeny of black or albino mothers, but not all brown mothers transmitted the inherited susceptibility to their progeny. (4) The incidence of cancer was significantly greater, in some groups, in the mice born in the third and later litters than in mice born in the earlier litters from the same mothers. (5) The incidence in the progeny was influenced also by the age at which the mothers developed mammary cancer.

It has previously been shown that a considerable proportion of mice of the so-called nonsusceptible stock developed mammary cancer when given the active milk agent. It is probable that some cancerous hybrid animals are likewise genetically nonsusceptible. Thus the tumor incidence would not represent the true percentage of susceptible animals, and should not serve as the only basis for a genetic interpretation of the data.

It is concluded that the inherited susceptibility for spontaneous mammary cancer in mice, as transmitted by mice of the cancerous A stock, probably depends upon multiple genetic factors, one of which may be linked with the gene for brown coat color.—Author's abstract.

Transplantation of Plant Tumors of Genetic Origin. White, P. R. [Rockefeller Inst. for Med. Research, Princeton, N. J.] *Cancer Research*, **4**:791-794. 1944.

Tumors were produced on healthy plants of *Nicotiana glauca*, a species that is never subject to spontaneous tumefaction, by implanting under the bark fragments of tissue cultures originally obtained from near the growing points of young plants of the hybrid *Nicotiana langsdorffii*×

N. glauca. The tissue cultures used had been maintained *in vitro* for 5 years and were isolated from plants that were healthy appearing but known to be subject to spontaneous tumefaction. The induced tumors were anatomically and histologically similar to those that appear spontaneously on the hybrid.

The writer considers the retention of the tumefacient property after 5 years *in vitro* and its expression in a non-tumefacient host as evidence of the fundamental character of this property, in this case a property of genetic origin.—Author's abstract.

The Serial Passage of an Avian Lymphoid Tumor. Olson, C., Jr. [Massachusetts Agric. Exper. Sta., Amherst, Mass.] *Cancer Research*, **4**:707-712. 1944.

The reaction of a chicken after receiving an implant of the lymphoid tumor will vary depending upon the activity potential of the tumor and the resistance of the host.

In ascending order of severity these reactions are: failure of the graft, growth and regression, progressive local growth only, growth with localized metastasis, and growth with diffuse metastasis.

Serial transfer of the tumor enhanced its ability to produce the more severe reactions.

Transfer of the tumor at 10 day intervals was more effective in raising the growth activity of the tumor than transfer at 15 day intervals.—Author's summary.

Beitrag zur Beziehung zwischen der Mitosegiftwirkung und der Konstitution von Colchicin Derivaten [Relation between the Antimitotic Effect of Colchicine Derivatives and their Constitution] Lettré, H., and Fernholz, H. [Rudolf Virchow-Krankenhaus, Berlin, Germany] *Ztschrft. f. physiol. Chem.*, **278**:175-200. 1943.

A series of derivatives of colchicine, mostly those obtained by Windaus and Cook in their investigations of the constitution of this substance, were tested as to their inhibitory effect on the growth of chicken heart fibroblasts in tissue culture and of the mouse ascites tumor. Thus the importance of certain atom groups in the colchicine molecule for the antimitotic effect could be established. The study was carried further by the determination of the antimitotic activity of synthetic products, similar in their structure to the "backbone" of the colchicine molecule. The phenyl-(*p*-methoxyphenyl) derivatives of methyl-, ethyl-, and propylmonoamines were investigated. Of these only the ethyl compound showed activity. From this it is concluded that the configuration: benzene ring-C-C-NH_2 is essential for the antimitotic action of colchicine and its derivatives.—Z. D.

Hemmung der Zellteilung durch östrogene Faktoren. [Inhibition of Cell Division by Estrogens.] Lettré, H. [Rudolf Virchow-Krankenhaus, Berlin, Germany] *Ztschrft. f. physiol. Chem.*, **278**:201-205. 1943.

Diethylstilbestrol inhibits completely the growth of chicken heart fibroblasts in tissue culture at a concentration of 150-200γ/cc. Even 40γ/cc. has some effect. The author assumes that this is due to an addition of NH_3 to the double bond of the ethyl bridge, because the addition product shows the atom grouping, phenyl-C-C-NH_2, which was recognized in a previous paper as antimitotic. Na_2 estradiol phosphate (Schering), a water-soluble ester of estradiol, at a concentration of 100γ/cc. gave a marked inhibition of culture growth. The author reports without giving experimental details that an oxidation product of adrenalin proved to be a "mitosis poison" in so small a concentration that it can be taken into consideration as a physiological antimitotic principle.—Z. D.

Mitosegifte aus der Steringruppe. (Vorläufige Mitteilung). [Mitosis Poisons in the Steroid Group (Preliminary Communication)] Lettré, H. [Rudolf Virchow-Krankenhaus, Berlin, Germany] *Ztschrft. f. physiol. Chem.*, **278**:206-207. 1943.

The monomethyl ester of the 7,17-diamino-3-hydroxy-estratriene-1,3,5 poisons mitosis in cultures of chicken heart fibroblasts at a concentration of 1γ/cc.—Z. D.

The Influence of Malignant Cells Upon the Growth of Fibroblasts *in Vitro*. Ludford, R. J., and Barlow, H. [Labs. of Imperial Cancer Research Fund, Mill Hill, England] *Cancer Research*, **4**:694-703. 1944.

The growth of mouse fibroblasts in tissue cultures is influenced by the proximity of other tissues.

A considerable stimulation of growth has been observed in the presence of the following tumors: (a) Spontaneous and transplanted mammary carcinomas of the high cancer strains Strong A, C3H, and RIII. (b) Mammary carcinomas induced in susceptible hybrids by the injection of dried RIII tumors.

Fibroblasts cultivated between 2 explants of these tumors grew more rapidly and were mitotically active over a longer period than those of control cultures, so that the maximum growth attained by cultures of the former was 8 to 10 times that of the controls in most experiments.

Fibroblastic growth was also stimulated to a lesser extent by cultures of embryo kidney and of the transplantable carcinoma 63. The latter is the most rapidly growing of the tumors employed in these experiments, hence it can be concluded that fibroblastic growth stimulation is not directly related to the rate of tumor growth.

Growth stimulation of fibroblasts occurs irrespective of: (a) their age, whether embryonic or adult; (b) their organ of origin, whether from heart, kidney, dermis, or mammary gland; (c) their genetic constitution, whether from high cancer or low cancer strains or from hybrids.

Sarcomas of both high mammary and low mammary cancer strains of mice inhibit fibroblastic growth under the experimental conditions described.—Authors' summary.

Transformation of Cells and Viruses. Haddow, A. [Royal Cancer Hosp. (Free), London, England] *Nature, London*, **154**:194-199. 1944.

A review.—E. L. K.

Heredity, Development and Infection. Darlington, C. D. [John Innes Horticultural Inst., London, England] *Nature, London*, **154**:164-169. 1944.

A review.—E. L. K.

Clinical and Pathological Reports

Recurrent Venous Thrombosis: An Early Complication of Obscure Visceral Carcinoma. Cooper, T., and Barker, N. W. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *Minnesota Med.*, **27**:31-36. 1944.

Visceral carcinoma is often the predisposing factor in the development of multiple, and sometimes distant, venous thrombosis. This seems particularly true in cases in which the neoplasm arises from or involves the body or tail of the pancreas. In the absence of other obvious causative factors, the development of apparently spontaneous peripheral thrombophlebitis in a case in which the patient is 50 or more years of age should suggest a careful search for visceral carcinoma. The formation of a thrombus in many of these instances would appear to be the result of more than simple mechanical obstruction, circulatory stasis, or alteration in the structure of the vessel wall. The authors suggest that further study of the factors influencing the coagulation of the blood are indicated.

Four case reports are presented.—J. L. M.

Skin and Subcutaneous Tissue

Calcified Epithelioma. Highman, B., and Ogden, G. E. [National Inst. of Health] *Arch. Path.*, **37**:169-174. 1944.

General discussion, based on a study of 11 specimens of calcified epithelioma gathered from 24,185 consecutive surgical specimens. The origin of such tumors remains obscure.—J. G. K.

Nervous System

Tumors of the Brain in Children and in Adolescents. A Clinical and Anatomic Survey of Ninety-Two Verified Cases. Globus, J. H., Zucker, J. M., and Rubinstein, J. M. [Mt. Sinai Hosp., New York, N. Y.] *Am. J. Dis. Child.*, **65**:604-663. 1943.

This study is based upon 92 cases of brain tumor occurring in children from 1 to 16 years of age. Certain departures from the clinical behavior observed in older groups are discussed.

The type of tumors prevalent in children and adolescents are autochthonous blastomatous growths, a fact that supports the view that cerebral neoplasms in the majority of instances probably originate from embryonal rests. Trauma is of no significance in precipitating or accelerating the growth of the tumor. Surgical intervention accomplishes much for the patients with a tumor of the hemangiomatous group and holds out fair promise to some with craniopharyngioma. The value of roentgen therapy cannot be estimated with any degree of accuracy on the basis of the small number of cases treated by radiation that are included in this study.—C. J. M.

Metastatic Brain Tumor with Bronchogenic Carcinoma as the Primary Source. Globus, J. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **10**:533-564. 1944.

The clinical manifestations and anatomical features of 18 cases of proved bronchogenic tumors with metastasis to the brain are recorded. Pulmonary signs and symptoms, in 2 cases, were absent throughout almost the entire clinical course; in 2 cases, they made their appearance after the development of cerebral manifestations. In 7 cases, they were already present in the early clinical course but were not confirmed by x-ray examination, while in 7 other cases, such signs and symptoms preceded cerebral manifestations and were confirmed by x-ray examination of the chest. In every instance of suspected brain tumor, x-ray examination of the chest should be carried out routinely. Metastasis to the brain, like carcinoma of the bronchus, is more frequent in males.—A. Cnl.

Clinical and Pathologic Features of Gliomas of the Spinal Cord. Shenkin, H. A., and Alpers, B. J. [Philadelphia, Pa.] *Arch. Neurol. & Psychiat.*, **52**:87-105. 1944.

A review of 27 verified cases of intramedullary gliomas of the spinal cord. The clinical features have been correlated with the pathologic findings in an attempt to clarify their diagnostic characteristics.—M. E. H.

Female Genital Tract

Two Granulosa-Celled Tumours. Friedmann, E. *Proc. Roy. Soc. Med.*, **37**:427. 1944.

Two granulosa-celled tumors are reported. In the first case a tumor the size of a fetal head developed in a girl aged 11 years with extreme uterine hypertrophy up to at least the size of a 16 weeks' pregnancy. In the second case, in a woman aged 74, a mixed type of granulosa-celled tumor developed with no uterine hypertrophy and no endometrial hyperplasia.—L. W. P.

A Case of Ovarian Dysgerminoma. Fraser, D. *Proc. Roy. Soc. Med.*, **37**:427. 1944.

A soft encapsulated tumor 3 in. in diameter produced an inhibitory hormone that caused secondary amenorrhea in a woman aged 36 with 2 children. After removal of the tumor the periods returned.—L. W. P.

A Solid Ovarian Teratoma. Green-Armytage, V. B., and Waller, R. G. L. *Proc. Roy. Soc. Med.*, **37**:435-436. 1944.

Report of a case in a woman aged 20, with a summary of the pathology of solid ovarian teratoma. The authors regard the present example, in which several types of tissue were represented without differentiation, as potentially malignant and liable to give rise to metastases via the blood stream, though the complete encapsulation present renders intraperitoneal implantation unlikely.—L. W. P

A Simple Office Test for Uterine Cancer Diagnosis. Ayre, J. E. [Royal Victoria Hosp., McGill, Univ., Montreal, Canada] *Canad. M. A. J.*, **51**:17-22. 1944.

The authors have extended the work of earlier investigators to include a smear of the external cervical os as well as a vaginal smear. A high degree of correlation was found when these smears were compared with smears from the growth itself and with tissue biopsies.—M. E. H.

Further Experience in the Management and Treatment of Carcinoma of the Fundus of the Uterus, with Five Year End Results in Seventy-Five Patients. Scheffey, L. C., Thudium, W. J., and Farell, D. M. [Jefferson Med. Coll. Hosp., Philadelphia, Pa.] *Am. J. Obst. & Gynec.*, **46**:786-802. 1943.

One hundred and twenty-seven cases of carcinoma of the uterine fundus have been studied with respect to diagnosis, management, and treatment. Seventy-five were suitable for a comparative analysis of 5 year end results. Data are given on age and menopausal relationship. Abnormal uterine bleeding was the most significant and reliable symptom in 96% of the entire series of patients. Diagnostic curettage was of great value, and no known ill effects followed its use. Fibromyomas were found in 38% of the patients treated surgically; palpation suggested the presence of fibroids in a number of irradiated patients. Carcinoma was thought to be limited to the uterus in 74% of the patients when first seen, irrespective of the size of the organ. Low-grade lesions responded equally well to irradiation and surgery; survival rate in intermediate and high-grade lesions was improved in cases in which irradiation had been a factor in treatment, either singly or in combination with surgery. Prognosis based on the grade of malignancy was uncertain. The 5 year end results were as follows: (a) treatment by surgery alone, 18.1% survival; (b) irradiation alone, 40.5%; (c) surgery and irradiation, 38.4% (corrected for uteri actually removed, 42.9%). Irrespective of the type of treatment, there was 38.6% absolute and 39.1% relative survival. It is concluded that preliminary irradiation with radium, followed by complete operation 8 to 10 weeks later, is the treatment of choice in carcinoma of the fundus uteri.—A. K.

Sarcoma of the Uterus. Randall, C. L. [Buffalo General Hosp., and Univ. of Buffalo, Buffalo, N. Y.] *Am. J. Obst. & Gynec.*, **45**:445-456. 1943.

The records of the Buffalo General Hospital from 1920 to 1941 inclusive list 3,686 uterine fibroids, 577 carcinomas, and 46 sarcomas (39 after reclassification) of the uterus. The authors believe that atypical cellularity of fibroids should not be considered alarming unless histologic changes justify the diagnosis of established sarcoma. The prognosis in uterine sarcoma depends primarily on the state of the disease when treatment is instituted and to a lesser degree on the histology of the tumor. A basis for the classification of these growths is presented as an aid in estimating the degree of clinical malignancy. The 5 year survival rate among 29 patients was 31%.—A. K.

The Importance of Increased Production and Excretion of Gonadotropic Hormone for Diagnosis of Hydatidiform Mole. Zondek, B. [The Rothschild-Hadassah-University Hosp., Jerusalem, Palestine] *J. Obst. & Gynaec. Brit. Emp.*, **49**:397-413. 1942.

A study of the diagnostic significance of prolans in urine, blood, and spinal fluid in cases of the various forms of hydatidiform mole, and of chorionepithelioma.—E. L. K.

Incidence, Treatment and Prevention of Hydatid Mole and Chorionepithelioma. Jeffreys, E. M., and Graffagnino, P. [Sch. of Med. Louisiana State Univ., and Charity Hosp. of Louisiana, New Orleans, La.] *West J. Surg.*, **52**:29-30. 1944.

The records of Charity Hospital show that the incidence of typical hydatid mole during the last 10 years among 85,453 pregnant women was 1 in 3,049 pregnancies. Seventy-five per cent of the patients were multiparous. In a previous paper 10 cases of chorionepithelioma that occurred during the period 1930 to 1940 were reported, and the authors add 4 cases observed since that time. Approximately 5% of cases of typical mole will develop chorionepithelioma. Proper treatment of hydatid mole includes thorough curettage, and careful follow-up studies should be maintained. A search for metastases by x-ray, complete hysterectomy, and bilateral salpingo-oophorectomy followed by deep x-ray therapy is the procedure of choice in cases in which chorionepithelioma is found.—M. E. H.

Carcinoma of the Uterine Cervix. Treatment and Prognosis. Morton, D. G. [Univ. of California Med. Sch., San Francisco, Calif.] *West. J. Surg.*, **52**:1-11. 1944.

A study of cases of carcinoma of the cervix treated at the University of California Hospital has lead the author to certain conclusions. Approximately 90% of cases are best treated by a combination of radium and roentgen irradiation. The latter should be given first unless the growth is small. Roentgen radiation has added materially to the percentage of survivals, probably by destroying cancer in the areas of primary spread that are inaccessible to radium. Age and the immediate gross reaction of the growth bear upon the prognosis in individual cases. Histological type is of no value in prognosis.—M. E. H.

Urinary System—Male and Female

The Interpretation of Certain Pathological Conditions of the Urogenital Tract on the Basis of Recent Advances in Embryology. Gruenwald, P. [Middlesex Univ., Sch. of Med., Waltham, Mass.] *Urol. & Cutan. Rev.*, **47**:306-320. 1943.

Certain phases of the development of the internal urogenital organs that have been investigated by descriptive and especially by experimental methods are reviewed from the viewpoint of developmental dynamics. The results of these studies are applied to the interpretation of various malformations and the common tumors of the urogenital organs.—V. F. M.

Lymphosarcoma of the Urinary Bladder. Rathbun, N. P., and Wehrbein, H. L. [Brooklyn, N. Y.] *J. Urol.*, **51**:31-36. 1944.

Multiple tumors removed from the bladder of a 64 year old female, who had a 10 year history of recurrent cystitis, proved to be lymphosarcoma. Only 5 other instances of lymphosarcoma of the bladder were found recorded in the literature. All the patients had a history of cystitis. The authors believe cystitis is prerequisite since without it no lymphoid tissue is present in the bladder. Possibly the neoplasm develops from secondary lymph follicles.—V. F. M.

Intrathoracic Tumors—Lungs—Pleura

Intrathoracic Tumors as a Problem in Diagnosis. Harrington, R. J. [Sioux City, Iowa] *J. Iowa M. Soc.*, **34**:45-59. 1944.

The clinical features of the more common forms of intrathoracic tumors are discussed. Ten cases are presented: 6 of bronchogenic carcinoma; 2 of mediastinal tumors, one proving to be lymphosarcoma and one a benign cyst; 1 case of a nonspecific pneumonitis re-

sembling bronchogenic carcinoma; 1 case with a large asymptomatic aortic aneurysm.—M. E. H.

Reasons for the Recent Increase of Bronchogenic Carcinoma. Boyd, W. [Univ. of Toronto, Toronto, Canada] *West. J. Surg.*, **52**:330-334. 1944.

The most important factor in the recent increased incidence reported for bronchial carcinoma is its better recognition by the clinician, radiologist, and pathologist. Various difficulties in diagnosis are discussed. Without denying the possibility that there may be a real increase in the incidence of the disease, it is suggested that improvement in diagnosis coupled with the increase in the span of life are sufficient reason for the apparent increase in bronchial carcinoma.—M. E. H.

Gastrointestinal Tract

Surgery of Malignant Tumors of the Cardiac End of the Stomach and of the Terminal End of the Esophagus. Dorsey, J. M. [Univ. of Illinois, Coll. of Med., Chicago, Ill.] *Surg. Clin. North Am.*, **24**:225-237. 1944.

A review covering the following subjects: pathology of gastric and esophageal carcinomas, importance of esophagoscopic biopsy, preoperative preparation, transthoracic operation, and differential diagnosis.—J. L. M.

Benign and Malignant Lesions of the Stomach. Allen, A. W. [Boston, Mass.] *Bull. New York Acad. Med.*, **20**: 15-24. 1944.

This is a presentation of the clinical features by means of which such benign conditions as ulcer, gastritis, polyps, syphilis, and leiomyoma can be distinguished from carcinoma, sarcoma, and lymphoma. Polyps were found to become malignant in 41% of the patients studied. Stress is laid on the short duration of symptoms in elderly persons and lesions located in prepyloric and fundal areas as being suggestive of malignant disease.—E. E. S.

Transthoracic Resection of the Cardia of the Stomach. Clagett, O. T., and Root, G. T. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:187-191. 1944.

One of the authors (Clagett) has explored lesions of the cardia of the stomach by the transthoracic route in 14 cases. In 8 instances gastric resection was carried out with 1 death occurring postoperatively. A case is presented in detail to emphasize the ever present possibility of extensive malignant neoplastic lesions in young people. It is also suggested that with the use of chemotherapy and minimal contamination during the operative procedure the thoracic incision often may be closed safely without any form of drainage.—J. L. M.

Prepyloric Lesions of the Stomach: Medical and Surgical Aspects. Jordan, S. M., and Lahey, F. H. [Lahey Clinic, Boston, Mass.] *Gastroenterology*, **1**:1-12. 1943.

A general discussion, with illustrative cases.—C. J. M.

The Life Cycle of Carcinoma of the Stomach. Feldman, M. [Baltimore, Md.] *Gastroenterology*, **2**:60-64. 1944.

Three patients are presented, each having a carcinoma of the stomach after a prolonged history of digestive disturbance of non-specific nature. The interpretation offered is that these patients suffered from very slowly growing carcinoma eventually giving rise to pyloric obstruction. It is suggested that more attention be paid to persistent digestive disorder no matter how mild.—E. E. S.

Tumors of the Stomach: A Case Study. Clark, D. E., and Jenkins, H. P. [Univ. of Chicago Sch. of Med., Chicago, Ill.] *Surg. Clin. North Am.*, **24**:60-78. 1944.

A group of selected cases is presented to illustrate many of the problems that arise in the handling of stomach lesions. The cases exemplify: (1) early carcinoma of stomach diagnosed as benign ulcer, (2) clinical diagnosis of carcinoma of stomach not demonstrable at operation, (3) early carcinoma of stomach revealed by exploration at cholecystectomy and importance of microscopic section in diagnosis, (4) malignant tumor of the stomach in an aged person, (5) leiomyosarcomas of stomach in a young man with presumed primary anemia, (6) filling defect suggesting a pedunculated tumor of the stomach but due to trichobezoar, (7) multiple benign polyps of the stomach treated by "sleeve" resection, (8) extensive carcinoma of stomach not revealed by x-ray and value of massive transfusions in extensive surgery, (9) successful removal of carcinoma of cardiac end of stomach by thoracolaparotomy in an aged person, (10) perforation of gastric wall during attempted gastroscopy.—J. L. M.

Pressure Defect in the Stomach Produced by Carcinoma of the Adrenal Glands, and Its Differentiation from Extramucosal Tumor of the Stomach. Alexander, R. E. (Vet. Admin., Bath, N. Y.) *M. Bull. Vet. Admin.*, **20**:341-343. 1944.

A case is presented in which the radiographic criteria indicated the presence of an extramucosal tumor of the stomach. It has been demonstrated that these criteria may be fulfilled by the presence of an extrinsic mass pressing upon the stomach. Careful fluoroscopic examination with observation of the mucosal folds overlying the defect should, in most instances, establish a definite differential diagnosis between these two conditions.—M. E. H.

Tumor of the Small Intestine as the Cause of Recurrent Melena. Report of Two Cases. Smith, L. A., Good, C. A., and Gray, H. K. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:117-122. 1944.

By presenting two case reports, the authors emphasize the fact that although there may be clinical evidence of a lesion from which hemorrhage may occur, the source of the hemorrhage may actually be some other lesion that has not been demonstrated. Therefore a diligent search should be made before performing a radical operation.—J. L. M.

Polypoid Carcinoma of the Ileum Producing Intussusception: Primary Resection with Recovery of Patient. Black, B. M. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:142-146. 1944.

A brief discussion and report of a case. The author believes that in the case described the polypoid carcinoma had been present in the patient for at least 10 years and that it had probably provoked many attacks of intusssusception all of which were followed by spontaneous recovery except the last attack. It was possible to resect the invaginated portion of the bowel and to restore the continuity of the intestinal tract by side-to-side ileocolostomy.—J. L. M.

Metastasizing Carcinoids of the Ileum. Dockerty, M. B., Ashburn, F. S., and Waugh, J. M. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:228-235. 1944.

Thirty cases of carcinoid tumor have been recorded at the Mayo Clinic between 1906 and 1943. Of these 13 in which metastasis was demonstrated either at operation or necropsy constitute the material of this report.

Although carcinoids are generally recognized as being benign, the tumors in these cases metastasized. Throughout the literature carcinoids are represented as being clinically silent; in 9 of these cases major gastrointestinal complaints were present. Carcinoids are ordinarily looked on as being native to the tip of the appendix; the tumors in this series involved primarily the ileum. Carcinoids are reported as occurring in the form of solitary tumors; 5 of these 13 cases presented multiple primary nodules.—J. L. M.

Carcinoid Tumors of the Appendix. King, W. W. [Denver, Colo.] *Rocky Mt. M. J.*, **41**:480-483. 1944.

A case report.—M. E. H.

Lymphosarcoma of the Cecum: Report of Case. Harper, S. B., Waugh, J. M., and Dockerty, M. B. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:182-186. 1944.

A case report showing that lymphosarcoma of the cecum lends itself to radical resection and carries as favorable a prognosis as lymphosarcoma occurring in any place in the gastrointestinal tract.—J. L. M.

Cancer of the Colon. Cave, H. [New York, N. Y.] *Bull. New York Acad. Med.*, **20**:255-263. 1944.

Pertinent anatomical and physiologic facts concerning the large bowel are mentioned to explain the characteristics of tumors in various portions of the colon. Owing to the great width of the cecum, growths here often attain considerable size and have broad ulcerated surfaces giving rise to hemorrhage and anemia. In the descending colon, the increasingly small caliber of the lumen accounts for the frequency of obstruction in this region causing considerable pain and constipation. The most valuable aid to diagnosis is said to be radiography. A discussion of therapy is included.—E. E. S.

Extending Surgery in the Treatment of Cancer of the Colon. Brunschwig, A. [Univ. of Chicago, Chicago, Ill.] *Surg. Clin. North Am.*, **24**:185-202. 1944.

A discussion with illustrative case reports.—J. L. M.

Succinylsulfathiazole (Sulfasuxidine) and the Elimination of the Mikulicz Operation. Behrend, M. [Jewish Hosp., and Mt. Sinai Hosp., Philadelphia, Pa.] *Surg. Clin. North Am.*, **24**:238-247. 1944.

The author believes that the use of succinylsulfathiazole has revolutionized surgical procedures performed on the colon and that a primary anastomosis may be carried out if the occasion demands it. The drug should be administered in large doses at least a week before operation and for 5 days afterward. Four cases without a death are presented.—J. L. M.

Polyposis of the Colon. Slaughter, D. P. [Univ. of Illinois Coll. of Med., Chicago, Ill.] *Surg. Clin. North Am.*, **24**:161-174. 1944.

A general review covering the following: incidence of polyposis of the colon, clinical types, pathology, symptoms, diagnosis, and treatment. Three case reports are presented. —J. L. M.

Pancreas

Pancreatic Carcinoma. Report of Two Cases with Unusual Symptoms. Smalley, R. E., and Esterman, G. B. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **18**:444-449. 1943.

Presentation and discussion of 2 cases. In one, hematemesis was among the chief complaints; in the other, fever.—J. L. M.

Pituitary

Adamantinoma of the Craniopharyngeal Duct. Occurrence in a Child Manifesting Marked Cachexia and Dyspituitarism of the Lorain Type. Conley, T. M. [Indianapolis City Hosp., Indianapolis, Ind.] *Am. J. Dis. Child.*, **61**:1275-1308. 1941.

A report of a case in a $6\frac{1}{2}$ year old girl, with a review of the symptoms occurring in children, the pathogenesis and treatment of the tumor.—C. J. M.

Pituitary Gigantism. Hurxthal, L. M. [Lahey Clinic, Boston, Mass.] *Lahey Clin. Bull.*, **3**:101-106. 1943.

Report of a case followed for 6 years and treated with hormones and roentgen rays. (See *J. Clin. Endocrinol.*, **3**:12-19. 1943).—M. E. H.

Further Observations on Gigantism. Hurxthal, L. M. [Lahey Clinic, Boston, Mass.] *Lahey Clin. Bull.*, **3**:136-142. 1943.

Further observations on a true pituitary giant previously reported (*Lahey Clin. Bull.*, **3**:101-106. 1943) are described. In addition a case of excessive growth in a boy of 15, without other distinguishing features of hyperpituitarism, is presented. There was a history of gigantism in a grandfather. The differential diagnosis is discussed.—M. E. H.

Acromegalic Gigantism without Enlarged Sella Turcica and Caused by Probable Pituitary Tumor. Hurxthal, L. M., and Horrax, G. [Boston, Mass.] *Lahey Clin. Bull.*, **3**:162-166. 1943.

The case reported presented unusual features, the most outstanding being a normal-sized sella turcica.—M. E. H.

Book Review

METASTASES. MEDICAL AND SURGICAL. Malford W. Thewlis, with a foreword by Hubert A. Royster. Charlotte Medical Press, Charlotte, N. C. 1944. 230 pages, 13 illustrations. Price $5.00.

The contents of this book are divided into six sections or chapters under the following headings: I. General Considerations. II. Neoplasms. III. Infections. IV. Infectious Diseases. V. Miscellany, and VI. Regional Metastases.

The first section is a brief general discussion of the subject of metastasis. The others consist of lists of the primary site of the disease process, organs to which it may metastasize, and areas or organs from which it may have come. No written explanation accompanies these lists. There are three full-page illustrations.

The general considerations section is filled with misleading or erroneous statements such as "Sudden hemiplegia . . . . may be due to a small neurofibroma of the spine, which in turn may be due to metastases from other areas, especially the lungs." "Fibrosarcoma rarely causes metastases." "Adenocarcinoma of the breast rarely causes metastases"—to mention a few of many.

The illustrations are too small, poorly drawn, and not explained by any text.

The lists of primary sites, areas to which a disease process may spread, and areas from which it may have come are puzzling to the person trying to read the book. For instance, under "Adamantinoma" are listed

A. Hyphophysis
Jaw, especially lower jaw
Lung
Lymph-nodes
Nasopharynx
Orbit
Pituitary gland
Tibia

C. Rarely metastasizes. Slow growth.
To: Glands, cervical
Lung
Ovary
Tibia

Does this mean the author believes this tumor to arise in all the sites listed under A? Why does he list hypophysis and pituitary separately?

It is not hard to find many mistakes in this section too. The inclusion of infections and infectious diseases as one-third of a book on metastases is surprising to one who is accustomed to consider the term virtually synonymous with "cancerous metastases."

To sum up, the book is difficult to understand, full of errors, and consequently of little value.

GRAY H. TWOMBLY

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